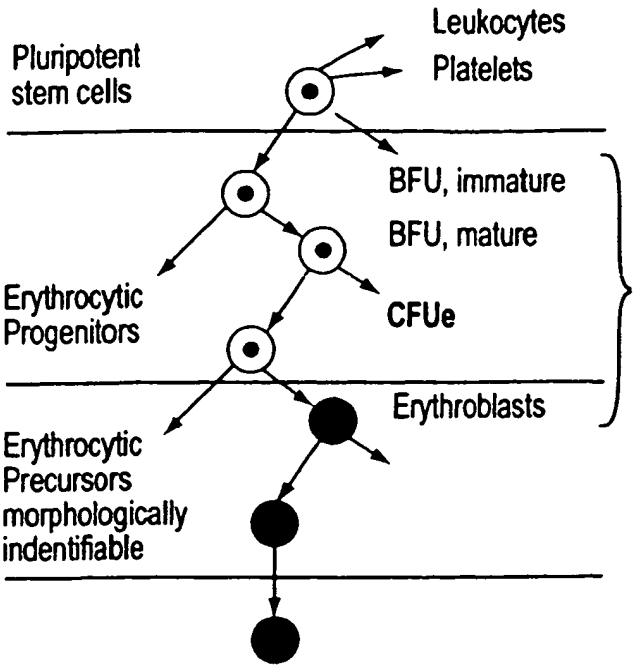
Erythropoiesis



EPO is believed to

- Stimulate the proliferation and differentiation of committed erythroid cells
- Prevent the apoptosis of erythrocytic progenitors
- Increase the viability of erythrocytes

FIG. 1

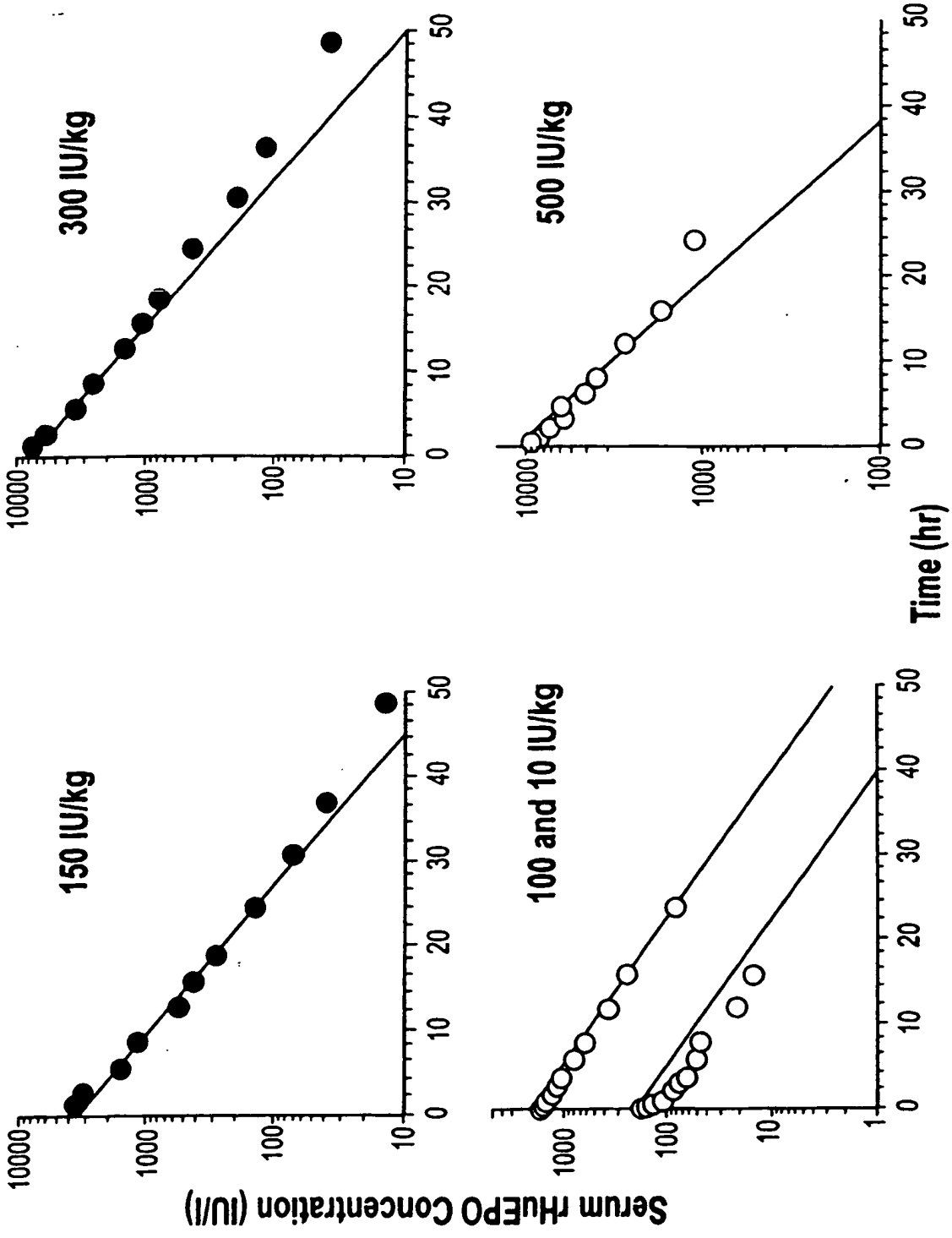

300 IU/kg
500 IU/kg
150 IU/kg
100 and 10 IU/kg
Serum rHuEPO Concentration (IU/l)
Time (hr)

FIG. 2

PHARMACOKINETIC PARAMETERS FOR INTRAVENOUS AND SUBCUTANEOUS EPO DOSES

PARAMETER	ESTIMATE	CV%
Vmax (IU/hr)	138.5	
Km (IU/l)	20940	
Vd (l/kg)	0.0558	
ka (hr^{-1})	0.0219	4.836
Fr	0.131	7.291
τ (Lower doses, hr)	44	
τ (Higher doses, hr)	60	

FIG. 3

PHARMACOKINETIC MODEL

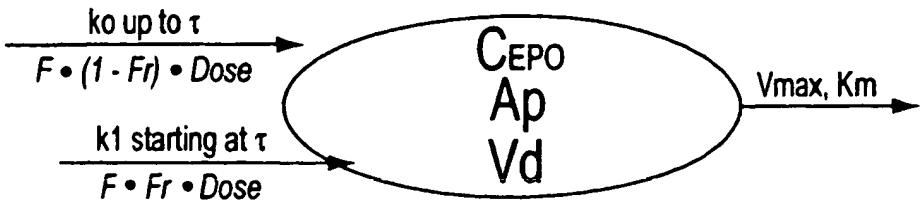


FIG. 4

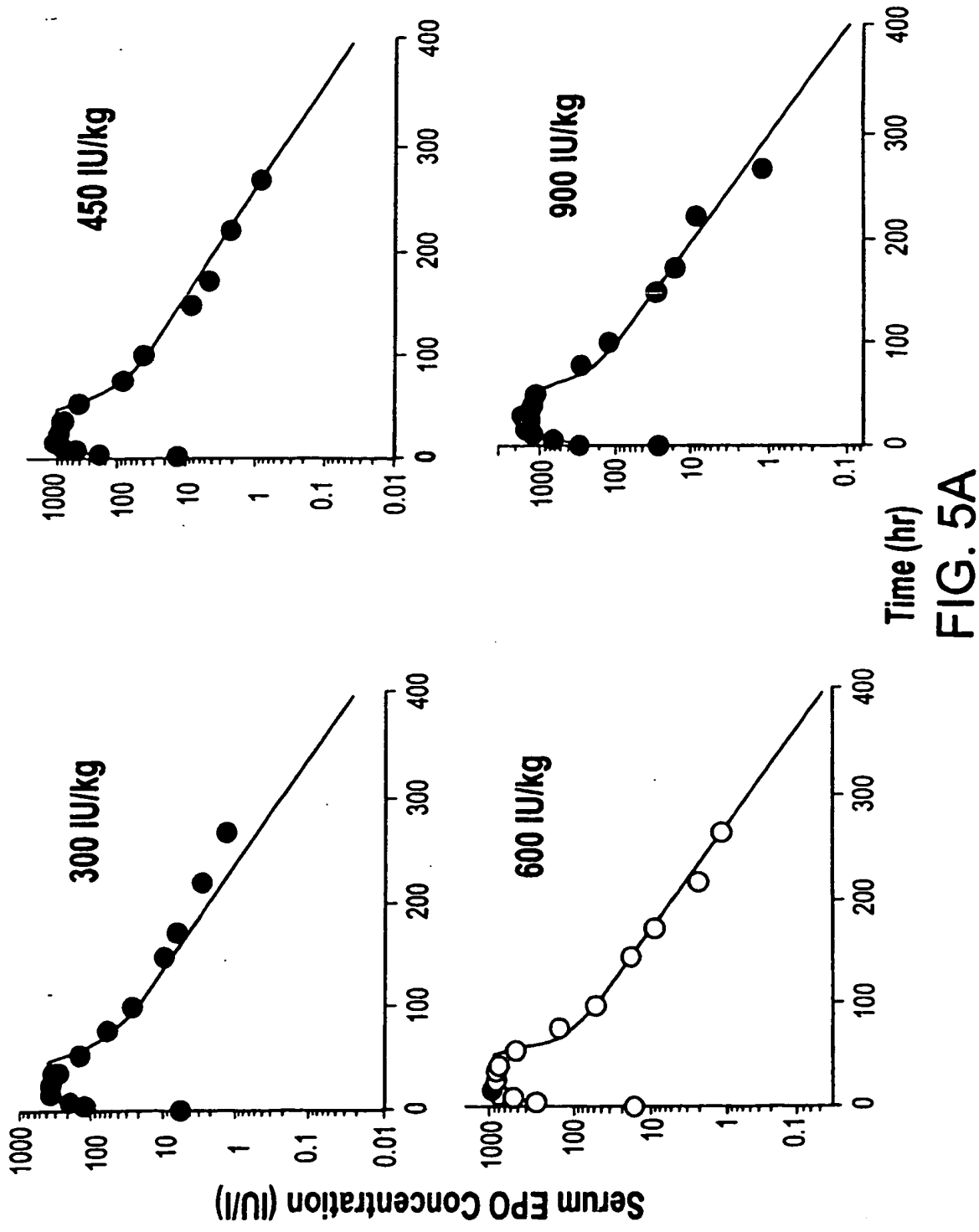

450 IU/kg
900 IU/kg
300 IU/kg
600 IU/kg
Serum EPO Concentration (IU/l)
Time (hr)
1000
100
10
1
0.1
0.01
0
100
200
300
400

FIG. 5A

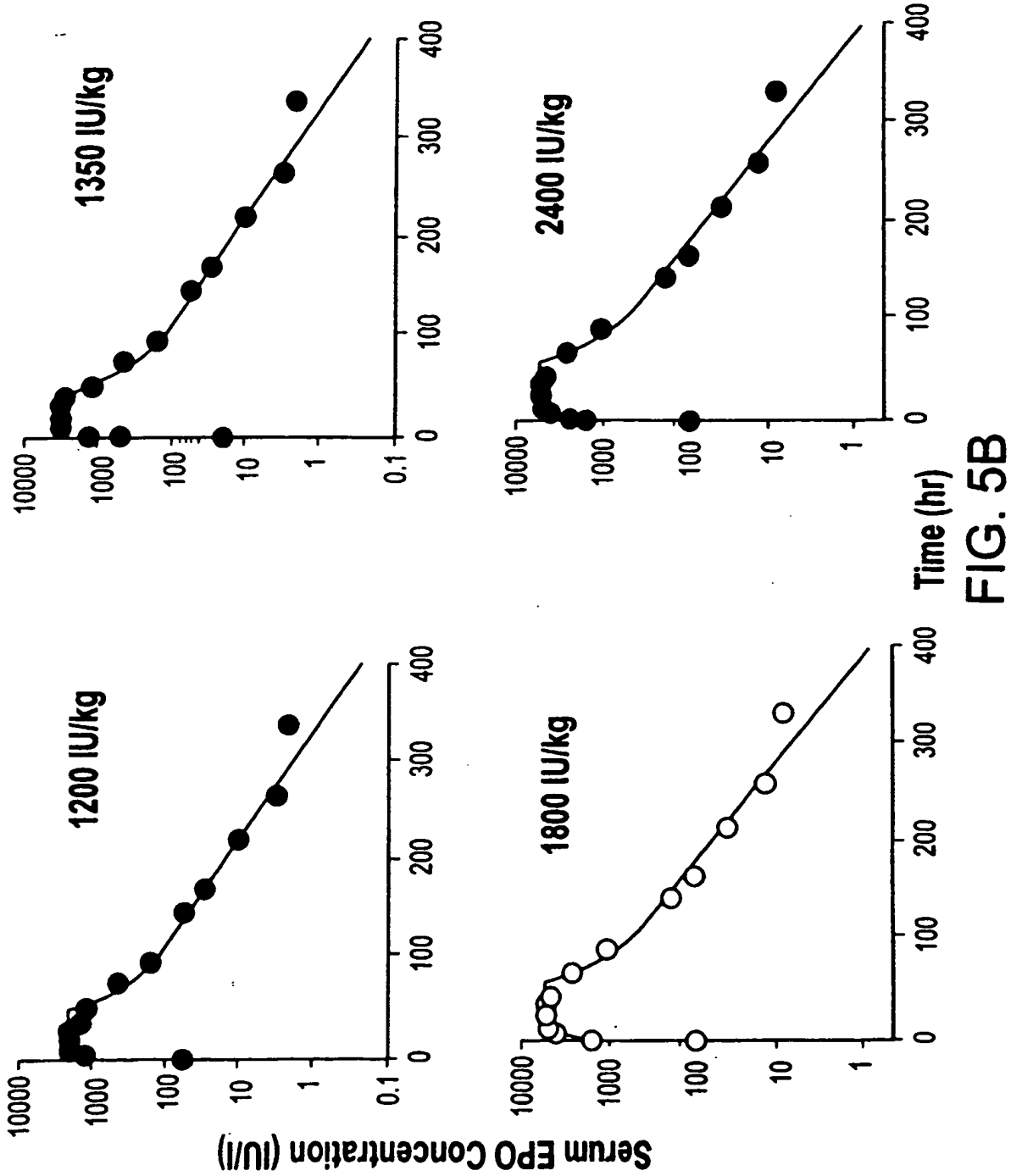

1350 IU/kg
2400 IU/kg
1200 IU/kg
1800 IU/kg
Serum EPO Concentration (IU/l)
Time (hr)
10000
1000
100
10
1
0.1
0
100
200
300
400

FIG. 5B

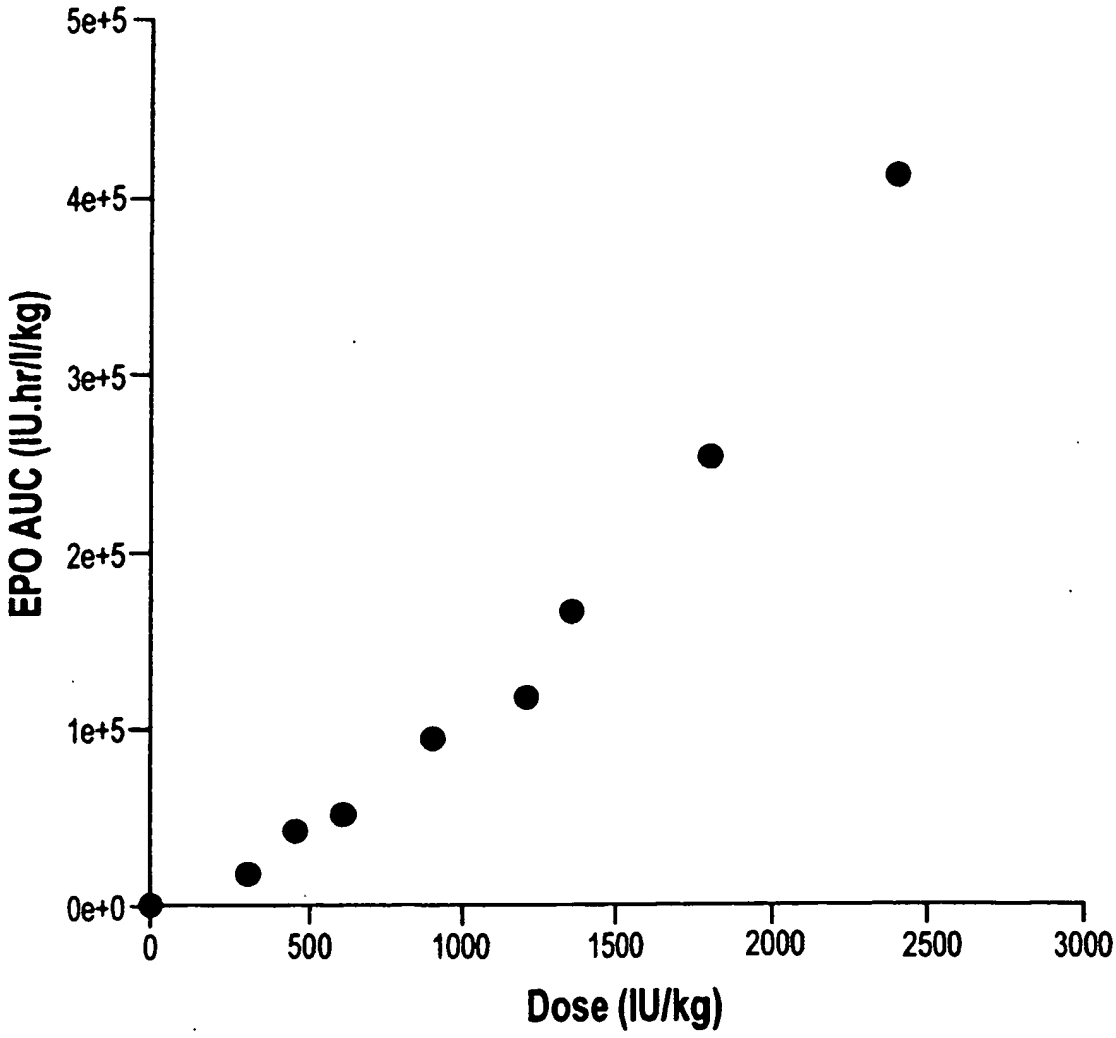

5e+5
4e+5
3e+5
2e+5
1e+5
0e+0
EPO AUC (IU.hr/l/kg)
0
500
1000
1500
2000
2500
3000
Dose (IU/kg)

FIG. 6

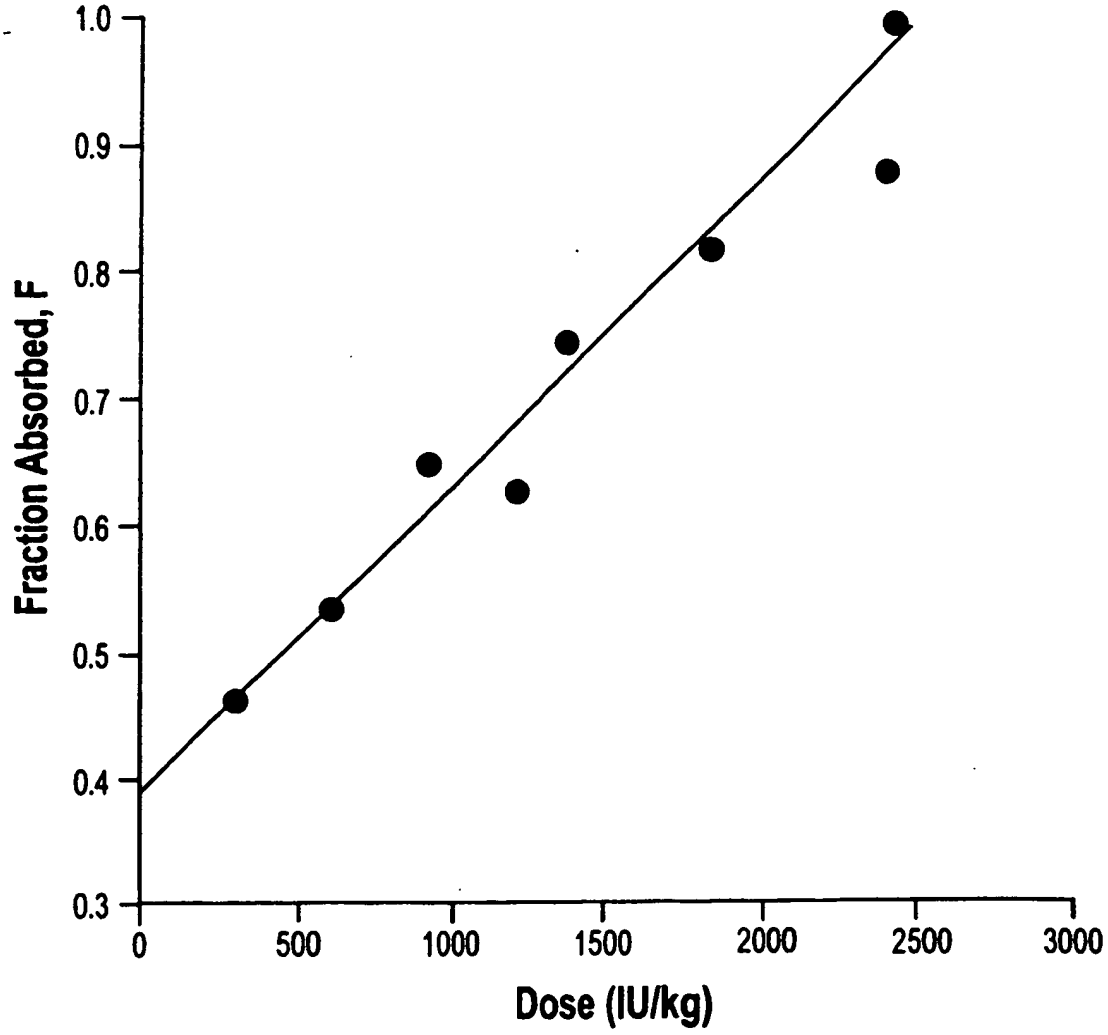

Fraction Absorbed, F
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0
500
1000
1500
2000
2500
3000
Dose (IU/kg)

FIG. 7

BIOAVAILABILITY VALUES FOR SUBCUTANEOUS EPO

DOSE (IU/kg)	F (fitted)	F (linear regression)	F (deconvolution)
300	0.464	0.463	0.36
450	0.614	0.50	0.56
600	0.535	0.538	0.51
900	0.651	0.613	0.61
1200	0.631	0.688	0.57
1350	0.748	0.752	0.73
1800	0.823	0.836	0.83
2400	1.00	0.987	1.00

FIG. 8

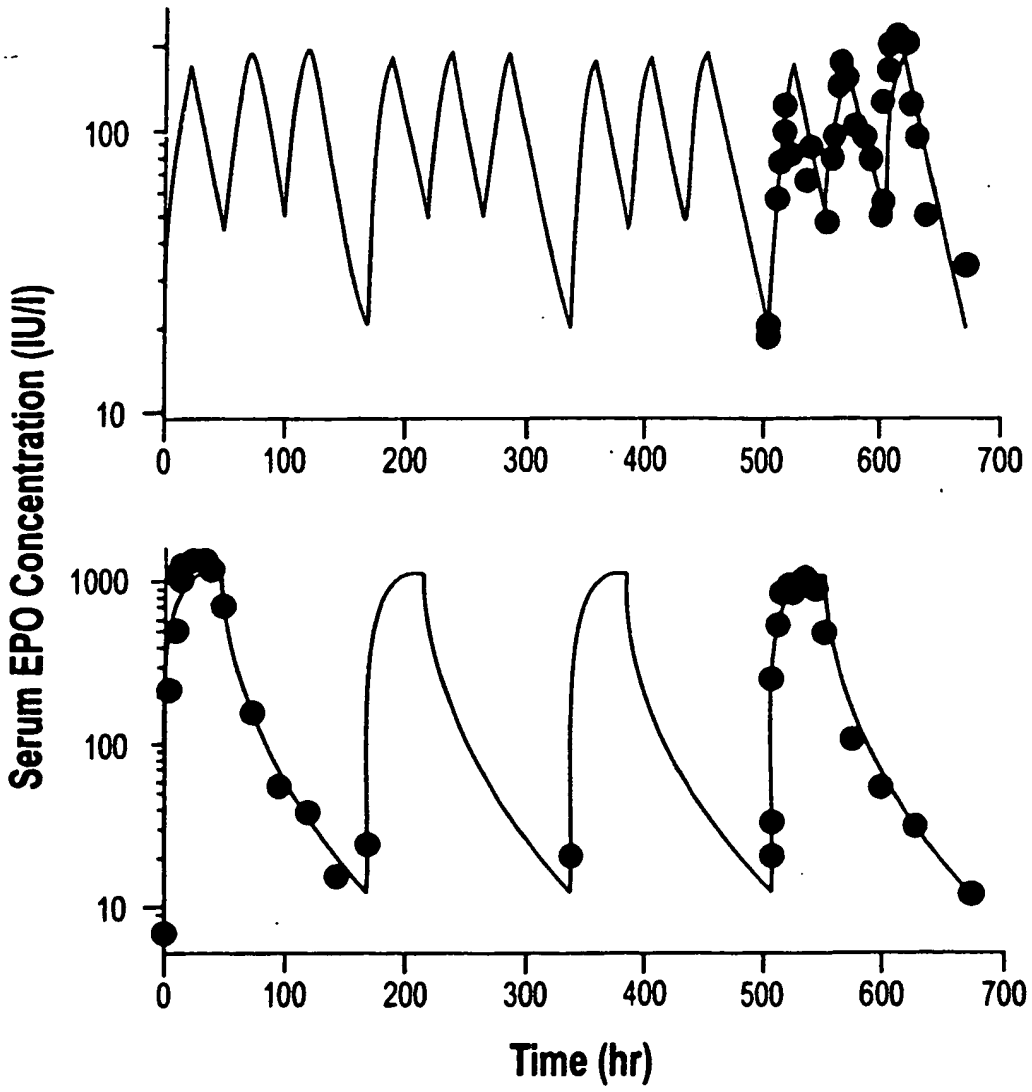

Serum EPO Concentration (IU/l)
100
10
0
100
200
300
400
500
600
700
1000
100
10
0
100
200
300
400
500
600
700
Time (hr)

FIG. 9

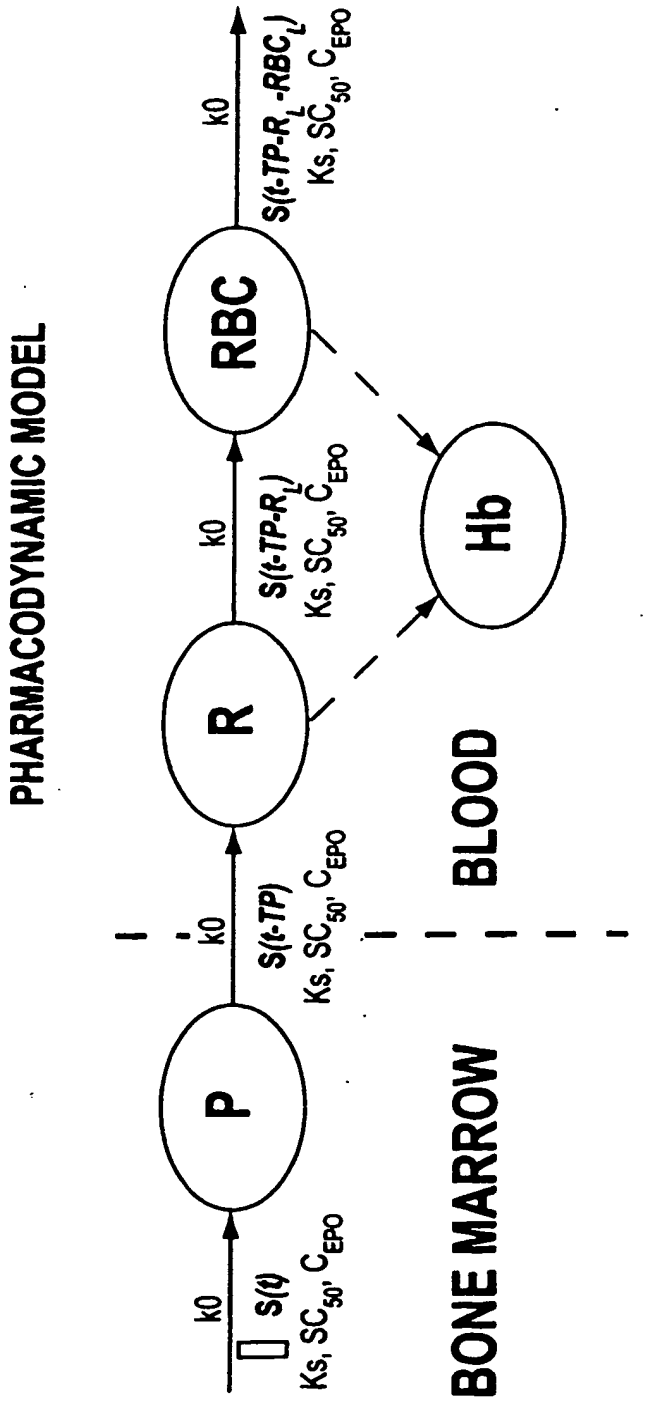

PHARMACODYNAMIC MODEL
BONE MARROW
BLOOD
P
R
RBC
Hb
k0
k0
k0
k0
S(t)
Ks, SC50, CEPO
S(t-TP)
Ks, SC50, CEPO
S(t-TP-RL)
Ks, SC50, CEPO
S(t-TP-RL-RBCL)
Ks, SC50, CEPO

FIG. 10

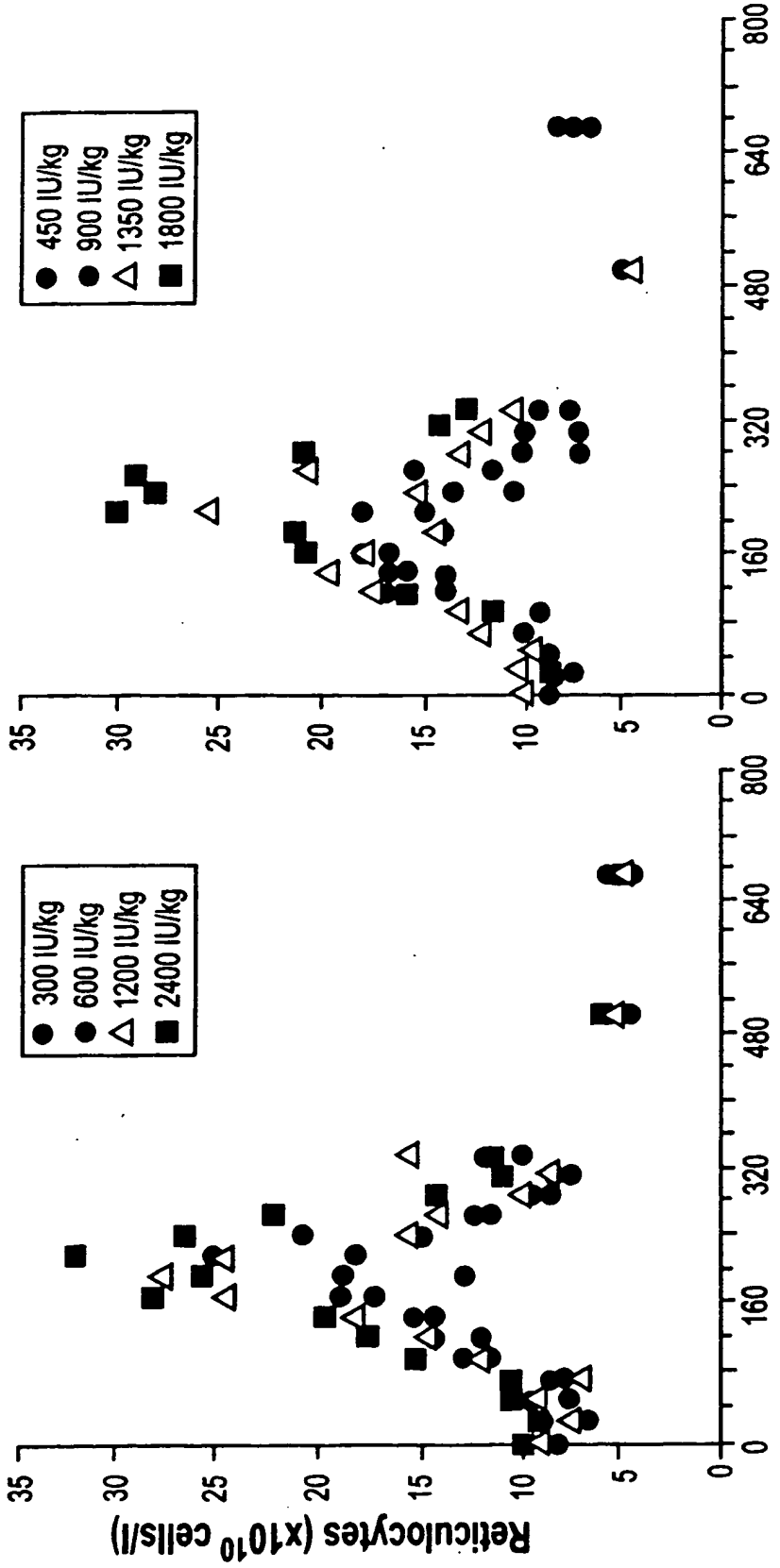

Reticulocytes (x10^10 cells/l)
Time (hr)
300 IU/kg
600 IU/kg
1200 IU/kg
2400 IU/kg
450 IU/kg
900 IU/kg
1350 IU/kg
1800 IU/kg

FIG. 11

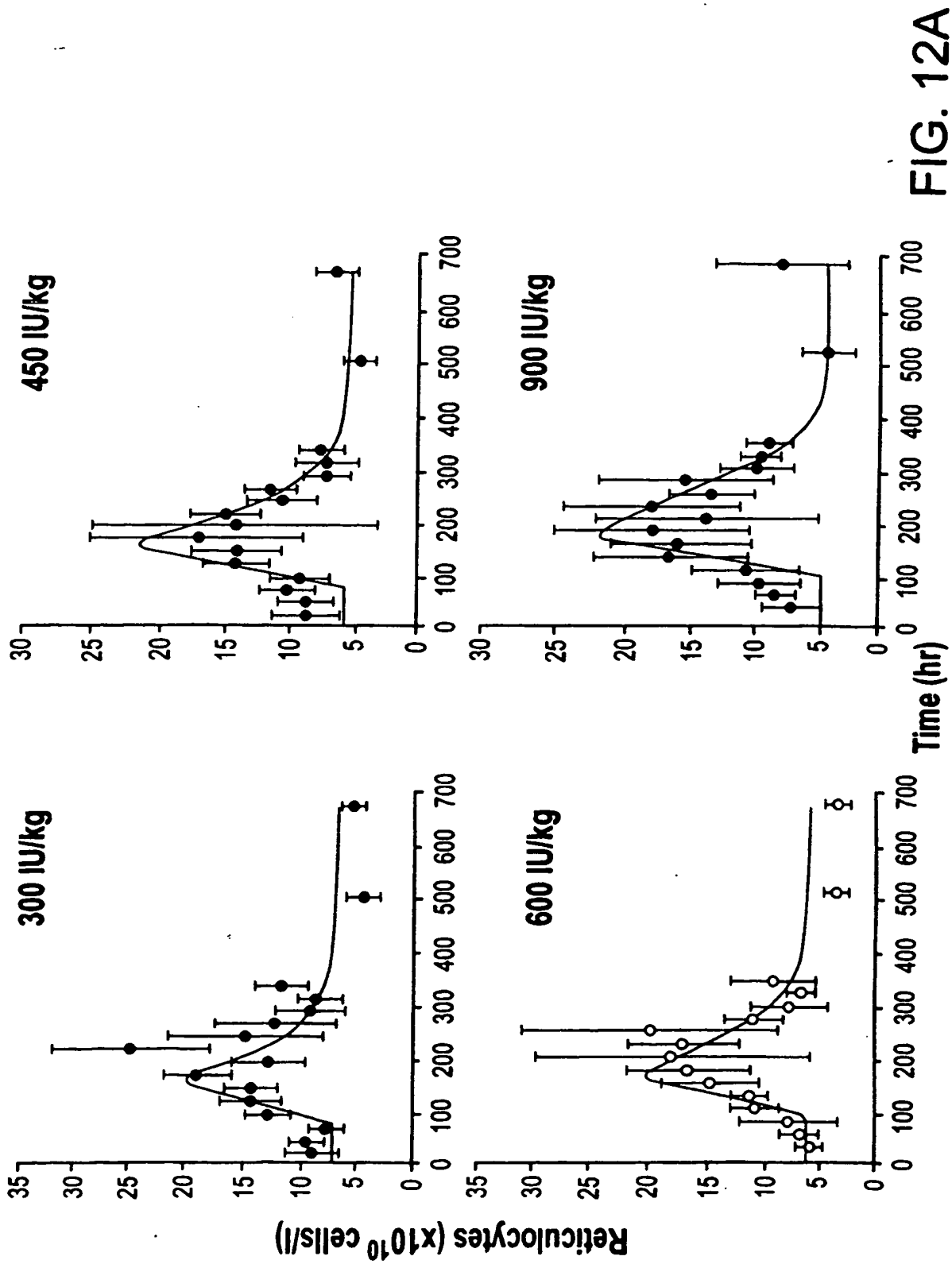

450 IU/kg
900 IU/kg
300 IU/kg
600 IU/kg
Reticulocytes (x10^10 cells/l)
Time (hr)

FIG. 12A

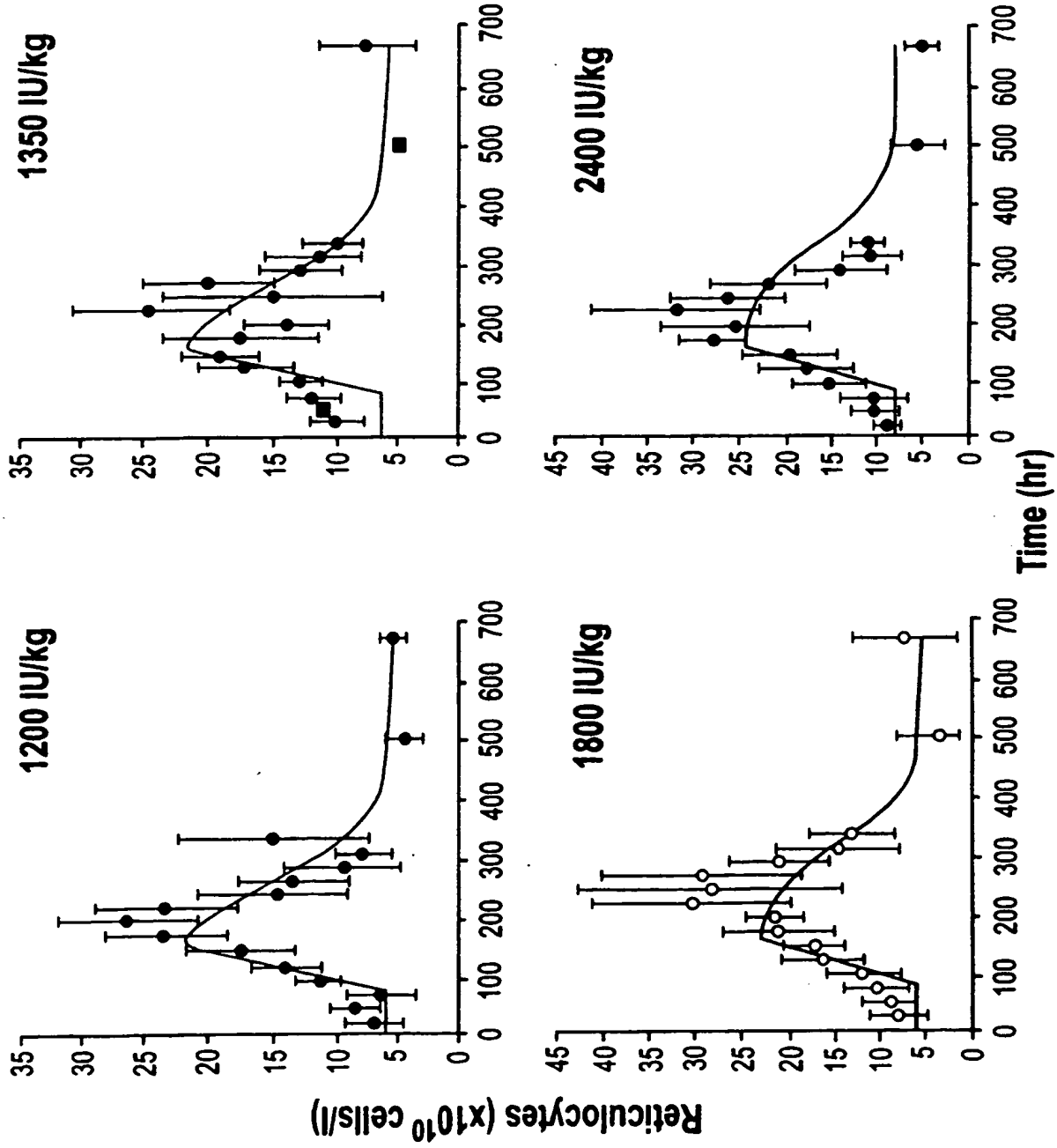

1350 IU/kg
2400 IU/kg
1200 IU/kg
1800 IU/kg
Reticulocytes (x10^10 cells/l)
Time (hr)

FIG. 12B

PHARMACODYNAMIC PARAMETERS FOR SUBCUTANEOUS EPO EFFECTS

	PARAMETER	ESTIMATE
ESTIMATED:	Ks (cells/l/hr)	0.3709×10^{10}
	SC50 (IU/l)	22.58
	TP (hr)	81.96
FIXED:		
	R_L (hr)	72
	RCB_L (hr)	2880
	Hb (pg/cell)	29.5
	Threshold (=SC50; IU/l)	22.58

FIG.13

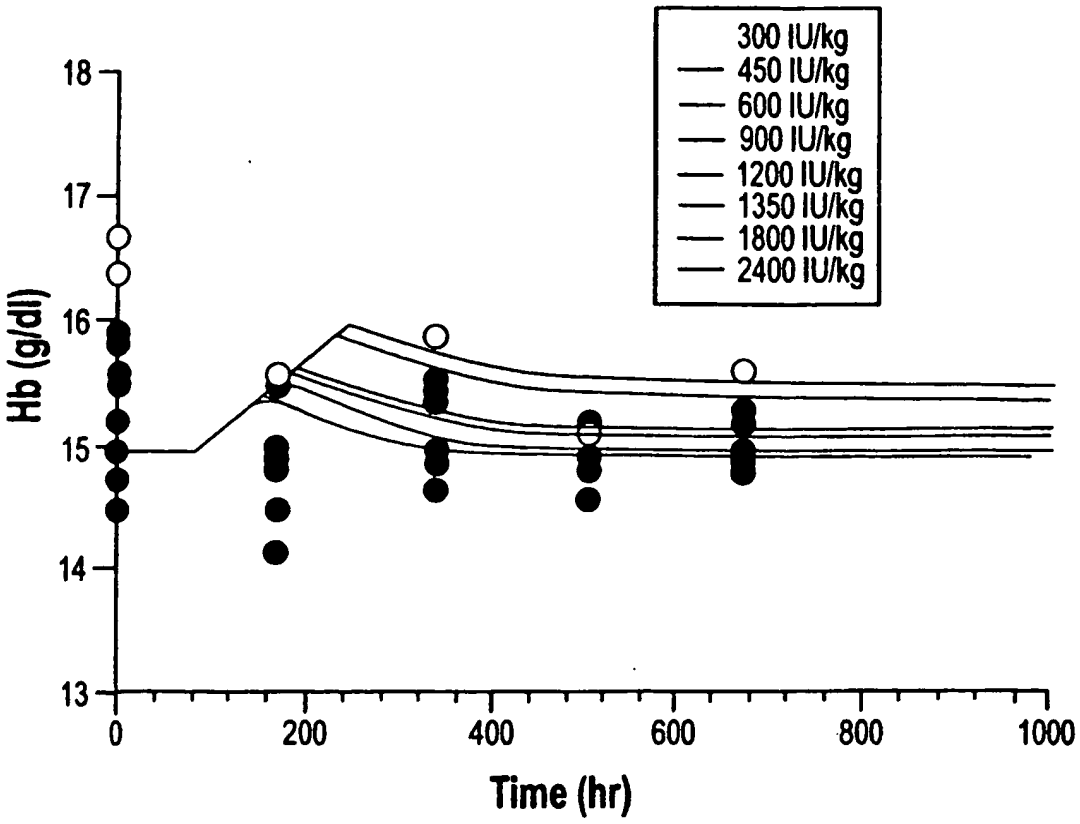

300 IU/kg
450 IU/kg
600 IU/kg
900 IU/kg
1200 IU/kg
1350 IU/kg
1800 IU/kg
2400 IU/kg
Hb (g/dl)
18
17
16
15
14
13
0
200
400
600
800
1000
Time (hr)

FIG. 14

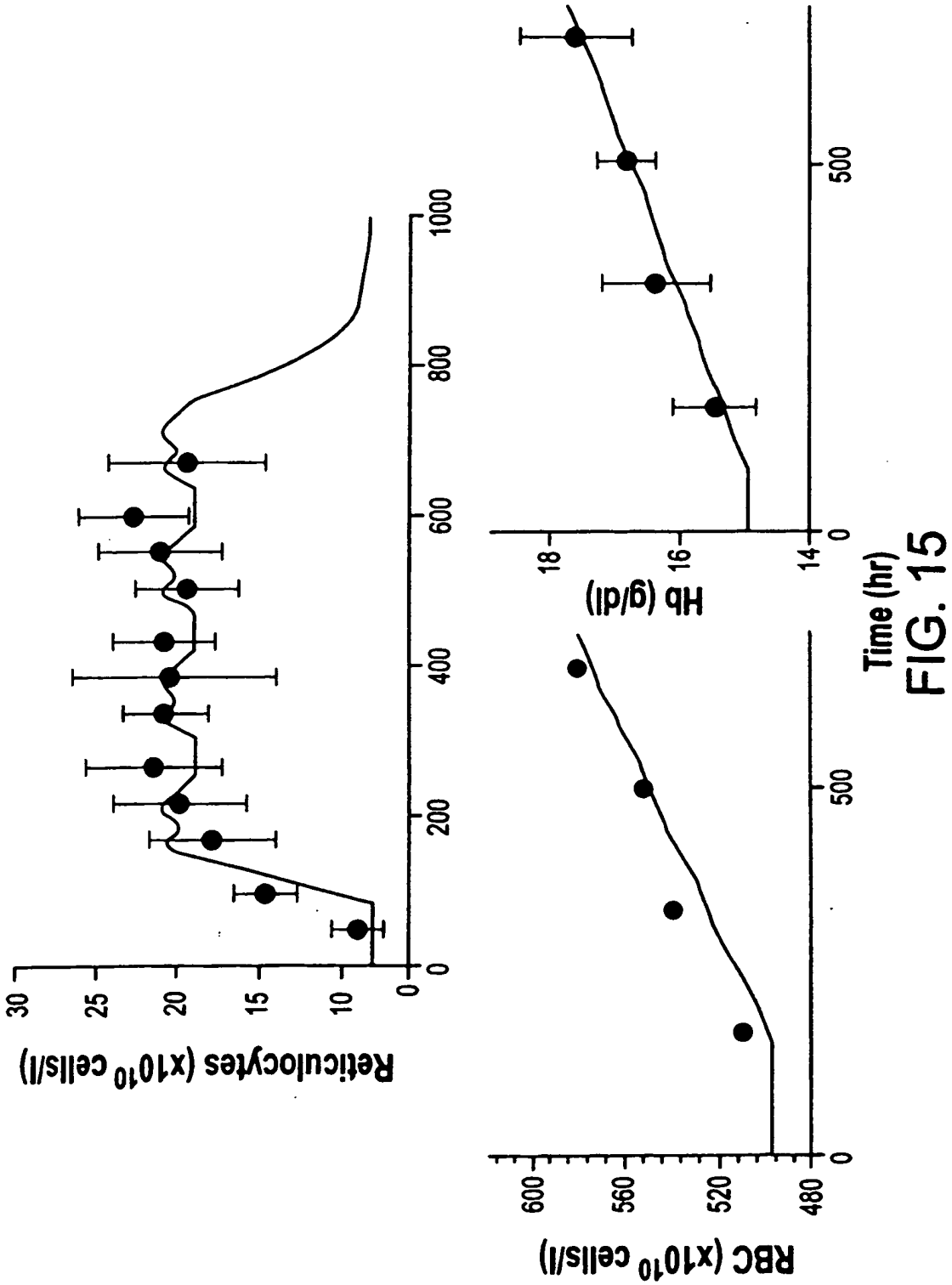

Reticulocytes (x10^10 cells/l)
0
10
15
20
25
30
0
200
400
600
800
1000
Hb (g/dl)
14
16
18
0
500
RBC (x10^10 cells/l)
480
520
560
600
0
500
Time (hr)

FIG. 15

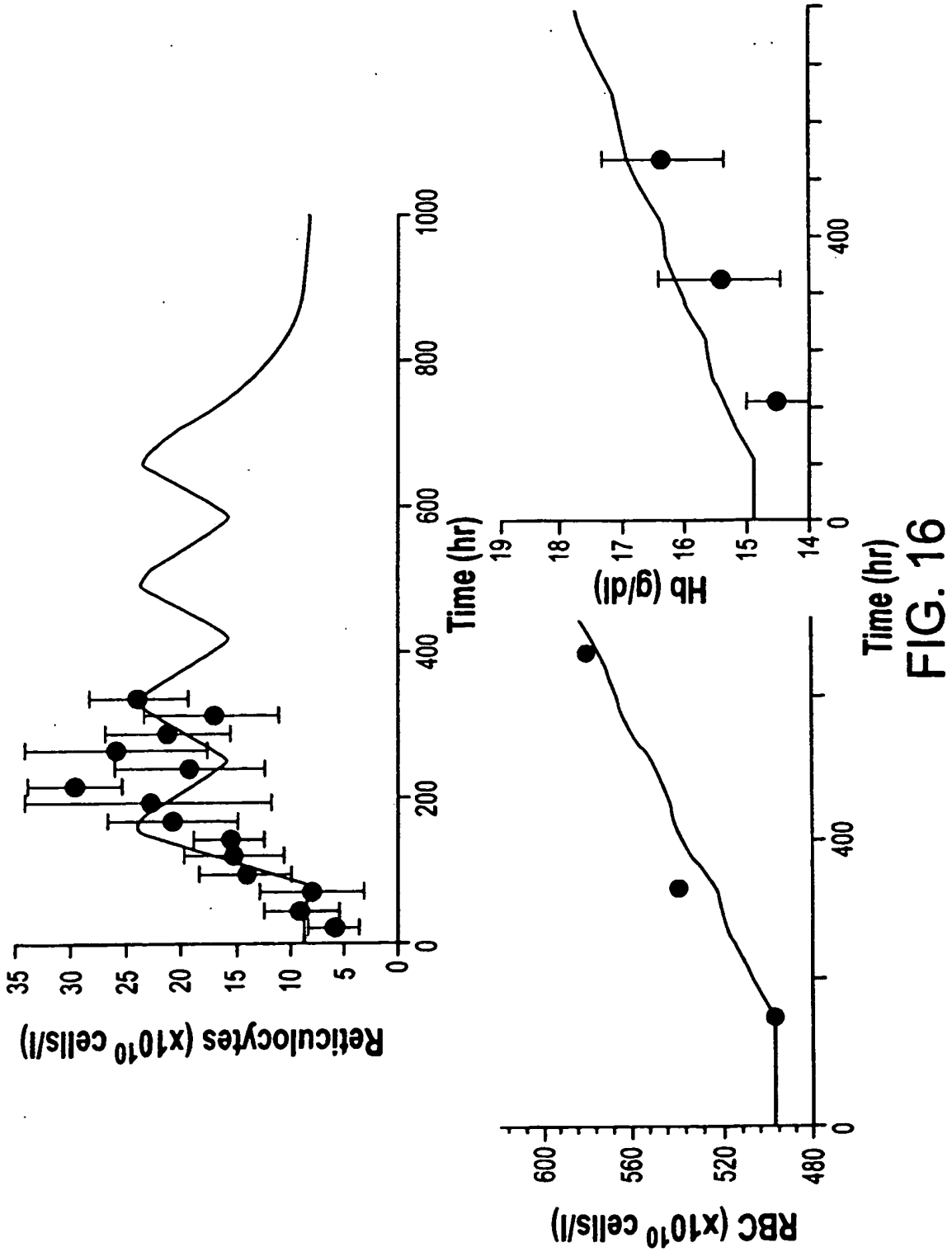

Reticulocytes (x10^10 cells/l)
0
5
10
15
20
25
30
35
0
200
400
600
800
1000
Time (hr)
Hb (g/dl)
14
15
16
17
18
19
0
400
Time (hr)
RBC (x10^10 cells/l)
480
520
560
600
0
400

FIG. 16

Study Type/Description	Study Identifier	Ref No.
Pharmacokinetics/Pharmacodynamics Single-center, open-label, parallel design, randomized study conducted in 36 healthy subjects (36 enrolled and analyzed for safety; 34 completed and analyzed for pharmacokinetic and pharmacodynamic [PK/PD]). Subjects were randomized to two treatment groups and received Epoetin alfa as either the standard cancer regimen (150 IU/kg s.c. t.i.w.) or a weekly fixed dose regimen (40,000 IU s.c. q.w.) for 4 wk.	EPO-PHI-373 (Pivotal)	1
Pharmacokinetics/Pharmacodynamics Single-center, open-label, parallel design, randomized study conducted in 49 healthy subjects (49 enrolled and analyzed for safety; 46 completed and analyzed for PK/PD). Subjects were randomized to two treatment groups and received Epoetin alfa as either the standard cancer regimen (150 IU/kg s.c. t.i.w.) or a weekly fixed dose regimen (40,000 IU s.c. q.w.) for 4 wk.	EPO-PHI-370 (Supportive)	2
Pharmacokinetics/Pharmacodynamics Open-label, randomized, placebo controlled, parallel-group, single-center study conducted in 32 subjects (32 enrolled and analyzed for safety; 30 completed and analyzed for PK/PD). Subjects were randomized into three treatment groups (N = 5 each) to receive one of the six treatments (450-, 900-, 1350-, and 1800-IU/kg single s.c. dose, and 150-IU/kg s.c. t.i.w. for 4 wk).	EPO-PHI-358 (Pilot exploratory)	3
Pharmacokinetics/Pharmacodynamics Open-label, randomized, placebo controlled, parallel-group, single-center study conducted in 30 subjects. Subjects were randomized into six treatment groups (N = 5 each) to receive one of the six treatments (300-, 600-, 1200-, and 2400-IU/kg single s.c. dose, and 600-IU/kg s.c. q.w. for 4 wk).	EPO-PHI-359 (Pilot exploratory)	4

FIG. 17

Applicant:	The R.W. Johnson Pharmaceutical Research Institute
Drug:	Epoetin Alfa Once Weekly Dosing
NDA No.:	Insert NDA No.

Study No (Ref No.)	Study Type	Dosage Form(s) Study Design	Dose	Batch No. Plant/Date Manufactured	No. of Subjects	Related IND or NDA No.s.	Submission Date	Applicant Conclusion	Previous Agency Responses on Study with Date of Correspondence
RWJPRI Clinical Study EPO-PHI-373 (1)	s.c.	10,000 IU/ml solution for s.c. injection (Formula FD 22512-000-T-45) 40,000 IU/ml solution for s.c. injection (Formula FD 22512-000-AA-45) Single-center, open-label, parallel-design, randomized study in healthy subjects. Two parallel treatment groups: 150 IU/kg s.c. t.i.w. x 4 wk and 40,000 IU q.w. x 4 wk.	150 IU/kg t.i.w. s.c. administration for 4 wk 40,000 IU q.w. s.c. administration for 4 wk	10,000 IU/ml formulation: 99KS077 Manufactured at Cilag AG Switzerland in Oct 1999 40,000 IU/ml formulation: 99KS091 Manufactured at Cilag AG< Switzerland in Oct 1999	36 enrolled 34 analyzed	NA	NA	Despite the difference in total exposure of erythropoietin in serum (AUC of Epoetin alfa) after the 150-IU/kg t.i.w. and the 40,000-IU q.w. dosing regimens, the hemoglobin responses to the two regimens were similar.	

FIG. 18A

Applicant:	The R.W. Johnson Pharmaceutical Research Institute
Drug:	Epoetin Alfa Once Weekly Dosing
NDA No.:	Insert NDA No.

Study No (Ref No.)	Study Type	Dosage Form(s) Study Design	Dose	Batch No. Plant/Date Manufactured	No. of Subjects	Related IND or NDA No.s	Submission Date	Applicant Conclusion	Previous Agency Responses on Study with Date of Correspondence
RWJPRI Clinical Study EPO-PHI-370 (2)	s.c.	10,000 IU/ml solution for s.c. injection (Formula FD 22512-000-C-45) 40,000 IU/ml solution for s.c. injection (Formula FD 22512-000-AC-45) Single-center, open-label, parallel-design, randomized study in healthy subjects. Two parallel treatment groups: 150 IU/kg s.c. t.i.w. x 4 wk and 40,000 IU q.w. x 4 wk.	150 IU/kg t.i.w. s.c. administration for 4 wk 40,000 IU q.w. s.c. administration for 4 wk	10,000 UI/ml formulation: Lot D000123 Manufactured at Amgen Inc., Thousand Oaks, CA 40,000 IU/ml formulation: Lot D000175 Manufactured at Amgen Inc., Thousand Oaks, CA	49 enrolled 46 analyzed	IND BB-IND-2318	Protocol 01 Jul 1999 Ammended Protocols	Despite the difference in total exposure of erythropoietin in serum (AUC of Epoetin alfa) after the 150-IU/kg t.i.w. and the 40,000-IU q.w. dosing regimens, the hemoglobin responses to the two regimens were similar.	

FIG. 18B

Applicant:	The R.W. Johnson Pharmaceutical Research Institute
Drug:	Epoetin Alfa Once Weekly Dosing
NDA No.:	Insert NDA No.

Study No (Ref No.)	Study Type	Dosage Form(s) Study Design	Dose	Batch No. Plant/Date Manufactured	No. of Subjects	Related IND or NDA No.s	Submission Date	Applicant Conclusion	Previous Agency Responses on Study with Date of Correspondence
RWJPRI Clinical Study EPO-PHI-358 (3)	s.c.	40,000 IU/ml solution for s.c. administration (Formula FD 22512-000-J-45) Open-label, randomized, placebo controlled, parallel-group, single center study conducted in 32 subjects (32 enrolled and analyzed for safety; 30 completed and analyzed for PK/PD). Subjects were randomized into six treatment	Single s.c. dose: 450, 900, 1350, 1800 IU/kg Multiple s.c. dose: 150 IU/kg t.i.w. for 4 wk	5C903J, Manufactured at Hoffman La-Roche, Basel Switzerland; March 1995	32 enrolled 30 analyzed	IND BB-IND-2318	Protocol 06 May 1996 Amended Protocol 06 May 1996	Pharmacological response to Epoetin alfa is a function of dose and dosing regimen. The absorption rate of Epoetin alfa after subcutaneous administration was independent of dose. Clearance of Epoetin alfa was dose-dependent - it decreased with increasing dose. There was an increasing trend of AUC of reticulocytes with AUC of Epoetin alfa for single doses. A continuous pharmacological response (a continuous production of reticulocytes and sustained elevation of	

FIG. 18C

Applicant:	The R.W. Johnson Pharmaceutical Research Institute							
Drug:	Epoetin Alfa Once Weekly Dosing							
NDA No.:	Insert NDA No.							
Study No (Ref No.)	Study Type	Dosage Form(s) Study Design	Dose	Batch No. Plant/Date Manufactured	No. of Subjects	Related IND or NDA No.s	Submission Date	Applicant Conclusion	Previous Agency Responses on Study with Date of Correspondence
		groups (N = 5 each) to receive one of the six treatments (placebo 450, 900, 1350, and 1800 IU/kg single dose, and 150 IU/kg t.i.w. for 4 wk).						hemoglobin) requires Epoetin alfa serum concentration to be maintained continuously (such as after 150 IU/kg t.i.w. dosing regimen) or intermittently (such as after the 600-IU/kg q.w. dosing regimen) above endogenous level.	

FIG. 18C

Applicant:	The R.W. Johnson Pharmaceutical Research Institute
Drug:	Epoetin Alfa Once Weekly Dosing
NDA No.:	Insert NDA No.

Study No (Ref No.)	Study Type	Dosage Form(s) Study Design	Dose	Batch No. Plant/Date Manufactured	No. of Subjects	Related IND or NDA No.s	Submission Date	Applicant Conclusion	Previous Agency Responses on Study with Date of Correspondence
RWJPRI Clinical Study EPO-PHI-359 (4)	s.c.	40,000 IU/ml solution for s.c. administration (Formula FD 22512-000-J-45) Open-label, randomized, placebo controlled, parallel-group, single center study conducted in healthy subjects. Subjects were randomized into six treatment groups (N = 5 each) to receive one of the six treatments (placebo 300,	Single s.c. dose: 300, 600, 1200, 2400 IU/kg Multiple s.c. doses: 600 IU/kg q.w. for 4 wk	5C903J, Manufactured at Hoffman La-Roche, Basel Switzerland; March 1995	30 enrolled 30 analyzed	IND BB-IND-2318	06 May 1996	Pharmacological response to Epoetin alfa is a function of dose and dosing regimen. The absorption rate of Epoetin alfa after subcutaneous administration was independent of dose. Clearance of Epoetin alfa was dose-dependent - it decreased with increasing dose. There was an increasing trend of AUC of reticulocytes with AUC of Epoetin alfa for single doses. A continuous pharmacological response (a continuous production of reticulocytes and sustained elevation of	

FIG. 18D

Applicant:	The R.W. Johnson Pharmaceutical Research Institute
Drug:	Epoetin Alfa Once Weekly Dosing
NDA No.:	Insert NDA No.

Study No (Ref No.)	Study Type	Dosage Form(s) Study Design	Dose	Batch No. Plant/Date Manufactured	No. of Subjects	Related IND or NDA No.s	Submission Date	Applicant Conclusion	Previous Agency Responses on Study with Date of Correspondence
		600, 1200, 2400 IU/kg and 600 IU/kg q.w. for 4 wk).						hemoglobin) requires Epoetin alfa serum concentration to be maintained continuously (such as after 150 IU/kg t.i.w. dosing regimen) or intermittently (such as after the 600-IU/kg q.w. dosing regimen) above endogenous level.	

FIG. 18D

Applicant:	The R.W. Johnson Pharmaceutical Research Institute					
Drug:	Epoetin Alfa Once Weekly Dosing					
NDA No.:	Insert NDA No.					
Study	Dose	C_{max} (mIU/mL)	t_{max} (h)	AUC[a] (mIU·h/mL)	CL/F (mL/h/kg)	$t_{1/2}$ (h)
Single Subcutaneous Dose Administration						
EPO359	300 IU/kg	429 ± 86 (20.0%)	22.8 ± 8.1 (36.5%)	20056 ± 4138 (20.6%)	15.5 ± 3.1 (20.2%)	68.2 ± 52.2 (76.6%)
EPO358	450 IU/kg	1263 ± 290 (23.0%)	15.6 ± 5.8 (37.0%)	45498 ± 12342 (27.1%)	10.4 ± 2.6 (24.9%)	24.2 ± 3.2 (13.2%)
EPO359	600 IU/kg	1263 ± 486 (38.5%)	27.6 ± 9.1 (33.0%)	55475 ± 16384 (29.5%)	11.8 ± 4.2 (35.5%)	29.3 ± 9.4 (32.0%)
EPO358	900 IU/kg	2235 ± 599 (26.8%)	22.2 ± 12.7 (57.0%)	103154 ± 28024 (27.2%)	9.36 ± 2.97 (31.7%)	36.0 ± 13.5 (37.3%)
EPO359	1200 IU/kg	2256 ± 710 (31.4%)	26.4 ± 7.8 (29.4%)	119932 ± 44217 (36.9%)	11.2 ± 4.2 (37.7%)	78.5 ± 95.4 (122%)
EPO358	1350 IU/kg	3755 ± 879 (23.4%)	23.4 ± 8.8 (37.8%)	174193 ± 41417 (23.8%)	8.23 ± 2.57 (31.3%)	33.4 ± 2.4 (7.2%)
EPO358	1800 IU/kg	4370 ± 1673 (38.3%)	28.8 ± 7.8 (27.2%)	258600 ± 101175 (39.1%)	7.64 ± 2.22 (29.1%)	32.4 ± 8.4 (25.9%)
EPO359	2400 IU/kg	6819 ± 764 (11.2%)	25.2 ± 6.2 (24.7%)	429441 ± 32139 (7.5%)	5.61 ± 0.44 (7.8%)	43.6 ± 25.9 (59.5%)
Multiple Subcutaneous Dose Administration						
EPO358 Wk 4	150 IU/kg t.i.w.	252 ± 71 (28.0%)	NA	16582 ± 4256 (25.7%)	28.7 ± 7.8 (27.1%)	25.9 ± 7.1 (27.2%)
EPO359 Wk 1	600 IU/kg q.w.	1502 ± 384 (25.6%)	21.6 ± 6.1 (28.5%)	63439 ± 10893 (17.2%)	9.70 ± 1.8 (18.1%)	28.3 ± 7.5 (26.3%)
EPO359 Wk 4	600 IU/kg q.w.	1278 ± 213 (16.6%)	24.0 ± 8.7 (36.4%)	50725 ± 6774 (13.4%)	12.0 ± 1.6 (13.2%)	28.1 ± 7.0 (24.9%)

FIG. 19

Applicant:	The R.W. Johnson Pharmaceutical Research Institute					
Drug:	Epoetin Alfa Once Weekly Dosing					
NDA No.:	Insert NDA No.					
Study	Dose	C_{max} (mIU/mL)	t_{max} (h)	AUC[a] (mIU·h/mL)	CL/F (mL/h/kg)	$t_{1/2}$ (h)
		Single Subcutaneous Dose Administration				
EPO370 Wk 4	150 IU/kg t.i.w.	191 ± 100 (52.3%)	NA	13446 ± 4374 (32.5%)	37.1 ± 12.3 (33.1%)	31.8 ± 13.4 (42.1%)
EPO370 Wk 4	40,000 IU q.w.	785 ± 427 (54.4%0)	18 ± 5 (29.4%)	30084 ± 13516 (44.9%)	23.2 ± 10.8 (46.5%)	39.3 ± 7.1 (18.1%)
EPO373 Wk 4	150 IU/kg t.i.w.	143 ± 54 (37.8%)	NA	8587 ± 1521 (17.7%)	54.1 ± 10.1 (18.7%)	19.4 ± 8.1 (41.5%)
EPO373 Wk 4	40,000 IU q.w.	861 ± 445 (51.7%)	16 ± 8 (45.6%)	25747 ± 9062 (35.2%)	24.7 ± 7.2 (29.1%)	15.0 ± 6.1 (40.9%)

[a] AUC(0-168h) during a dose week for multiple dose regimens and AUC(0-672h) during the 4-wk of study period for single doses.

NA = Not applicable

FIG. 19

Applicant: The R.W. Johnson Pharmaceutical Research Institute Drug: Epoetin Alfa Once Weekly Dosing NDA No.: Insert NDA No.				
Study No. Primary Supportive (Ref. No.)	Type of Biological Fluid	Analysis Method	Sensitivity of Method Range (mU/mL)	Specificity of Assay
EPO-PHI-358 Pilot /Exploratory	Serum	RIA (RWJPRI)[23]	7.8-125	Detects both endogenous and exogenous EPO
EPO-PHI-359 Pilot /Exploratory	Serum	RIA (RWJPRI)[23]	7.8-125	Detects both endogenous and exogenous EPO
EPO-PHI-370 Supportive	Serum	RIA (PPD)[24]	7.8-125	Detects both endogenous and exogenous EPO
EPO-PHI-373 Pivotal	Serum	ELISA (PPD)[25]	7.8-125	Detects both endogenous and exogenous EPO

FIG. 20

Mean ± SD Demographic and Baseline Parameters for Subjects Enrolled in Clinical Studies EPO-PHI-358 and EPO-PHI-359

Parameter	EPO-PHI-358 (N=32)	EPO-PHI-359 (N=30)
Age (yr)	35.7 ± 7.25	34.1 ± 6.76
Weight (kg)	76.7 ± 7.10	77.7 ± 8.83
Height (cm)	174.2 ± 7.69	174.7 ± 7.88
Race		
White	8 (25%)	9 (30%)
Black	4 (13%)	1 (3%)
Asian	0 (0%)	1 (3%)
Hispanic	20 (63%)	19 (63%)

FIG. 21

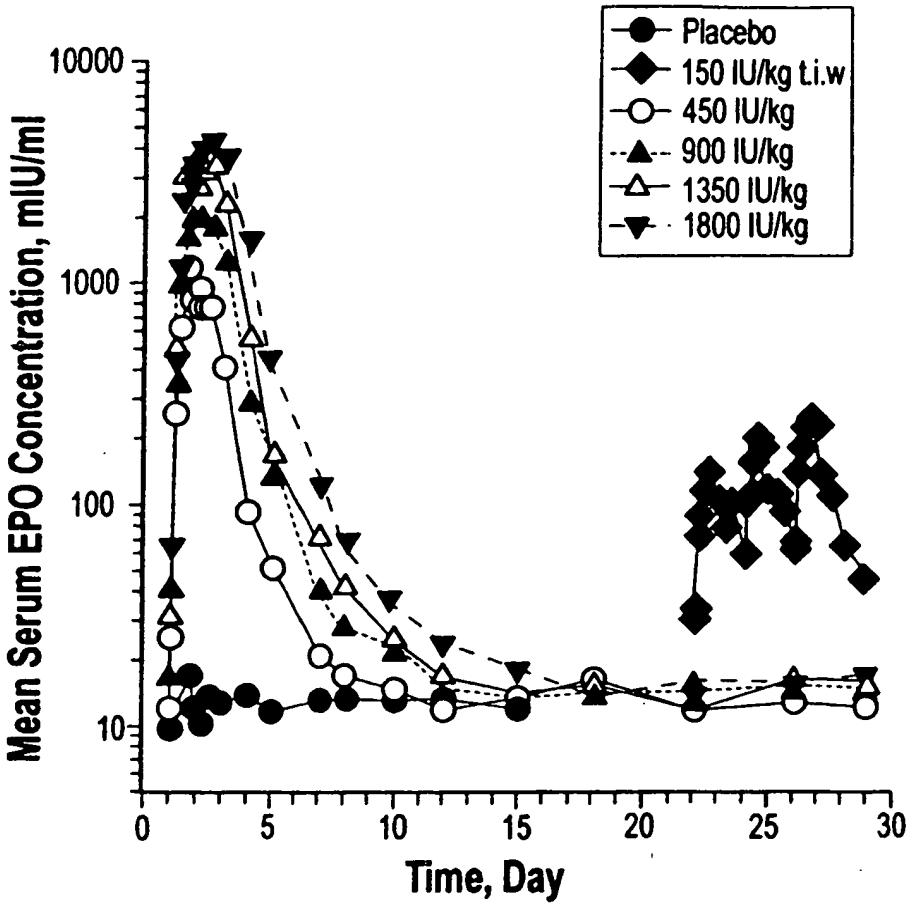

Placebo
150 IU/kg t.i.w
450 IU/kg
900 IU/kg
1350 IU/kg
1800 IU/kg
Mean Serum EPO Concentration, mIU/ml
10000
1000
100
10
0
5
10
15
20
25
30
Time, Day

FIG. 22

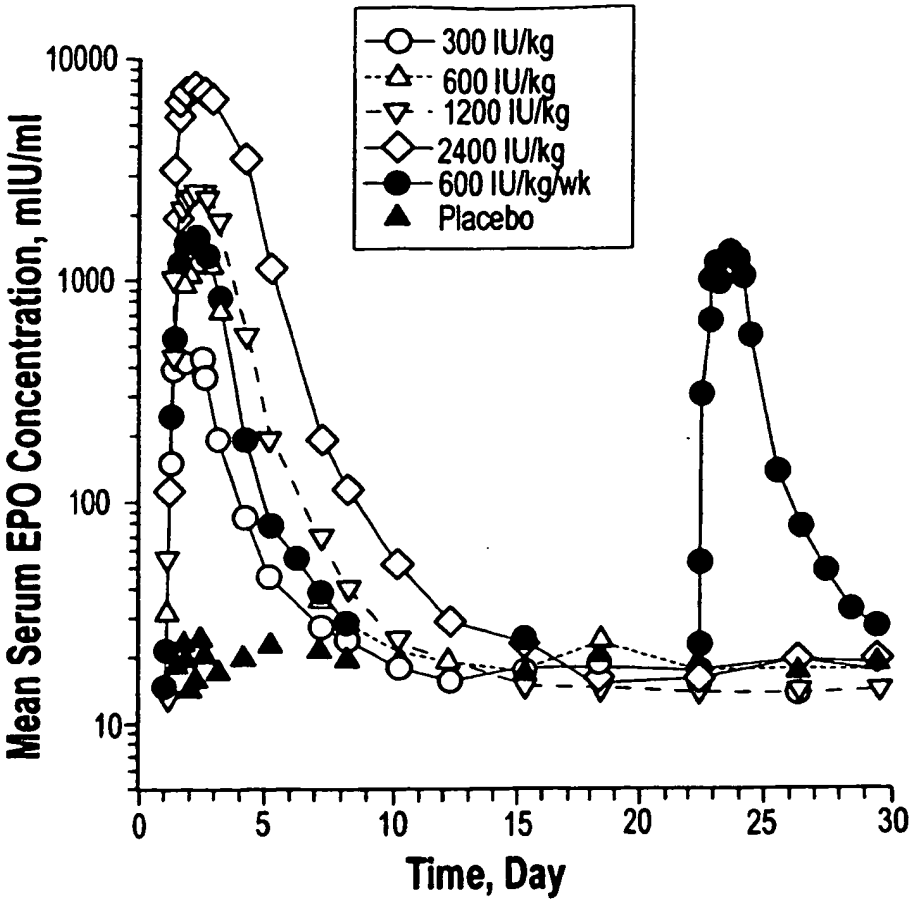

300 IU/kg
600 IU/kg
1200 IU/kg
2400 IU/kg
600 IU/kg/wk
Placebo
Mean Serum EPO Concentration, mIU/ml
10000
1000
100
10
0
5
10
15
20
25
30
Time, Day

FIG. 23

Mean ± SD (%CV) Pharmacokinetic and Pharmacodynamic Parameters (Clinical Studies EPO-PHI-358 and EPO-PHI-359)

Study	Dose	C_{max} (mIU/mL)	t_{max} (h)	AUC[a] (mIU·h/mL)	CL/F (mL/h/kg)	$t_{1/2}$ (h)	%RETI[b] AUC (%•h)
EPO359	300 IU/kg	429 ± 86 (20.0%)	22.2 ± 8.1 (36.5%)	20056 ± 4138 (20.6%)	15.5 ± 3.1 (20.2%)	68.2 ± 52.2 (76.6%)	1280 ± 157 (12.3%)
EPO358	450 IU/kg	1263 ± 290 (23.0%)	15.6 ± 5.8 (37.0%)	45498 ± 12342 (27.1%)	10.4 ± 2.6 (24.9%)	24.2 ± 3.2 (13.2%)	1191 ± 164 (13.8%)
EPO359	600 IU/kg	1263 ± 486 (38.5%)	27.6 ± 9.1 (33.0%)	55475 ± 16384 (29.5%)	11.8 ± 4.2 (35.5%)	29.3 ± 9.4 (32.0%)	1224 ± 227 (18.5%)
EPO358	900 IU/kg	2235 ± 599 (26.8%)	22.2 ± 12.7 (57.0%)	103154 ± 28024 (27.2%)	9.36 ± 2.97 (31.7%)	36.0 ± 13.5 (37.3%)	1296 ± 274 (21.1%)
EPO359	1200 IU/kg	2256 ± 710 (31.4%)	26.4 ± 7.8 (29.4%)	119932 ± 44217 (36.9%)	11.2 ± 4.2 (37.7%)	78.5 ± 95.4 (122%)	1413 ± 315 (22.3%)
EPO358	1350 IU/kg	3755 ± 879 (23.4%)	23.4 ± 8.8 (37.8%)	174193 ± 41417 (23.8%)	8.23 ± 2.57 (31.3%)	33.4 ± 2.4 (7.2%)	1406 ± 146 (10.4%)
EPO358	1800 IU/kg	4370 ± 1673 (38.3%)	28.8 ± 7.8 (27.2%)	258600 ± 101175 (39.1%)	7.64 ± 2.22 (29.1%)	32.4 ± 8.4 (25.9%)	1679 ± 407 (24.2%)
EPO359	2400 IU/kg	6819 ± 764 (11.2%)	25.2 ± 6.2 (24.7%)	429441 ± 32139 (7.5%)	5.61 ± 0.44 (7.8%)	43.6 ± 25.9 (59.5%)	1720 ± 233 (13.5%)
EPO358 Wk 4	150 IU/kg t.i.w.	252 ± 71 (28.0%)	NA	16582 ± 4256 (25.7%)	28.7 ± 7.8 (27.1%)	25.9 ± 7.1 (27.2%)	

FIG. 24

Mean ± SD (%CV) Pharmacokinetic and Pharmacodynamic Parameters (Clinical Studies EPO-PHI-358 and EPO-PHI-359)

Study	Dose	C_{max} (mIU/mL)	t_{max} (h)	AUC[a] (mIU·h/mL)	CL/F (mL/h/kg)	$t_{1/2}$ (h)	%RETI[b] AUC (%·h)
EPO358 Wk 1-4	150 IU/kg t.i.w.						1749 ± 406 (23.2%)
EPO359 Wk 1	600 IU/kg/wk	1502 ± 384 (25.6%)	21.6 ± 6.1 (28.5%)	63439 ± 10893 (17.2%)	9.70 ± 1.8 (18.1%)	28.3 ± 7.5 (26.3%)	
EPO359 Wk 4	600 IU/kg/wk	1278 ± 213 (16.6%)	24.0 ± 8.7 (36.4%)	50725 ± 6774 (13.4%)	12.0 ±1.6 (13.2%)	28.1 ± 7.0 (24.9%)	
EPO359 Wk 1-4	600 IU/kg/wk						2220 ± 493 (22.2%)

[a] AUC(0-168) during a dosing week for multiple dose regimens and AUC(0-672) during the 4 wk of study period for single doses.

[b] Percent reticulocyte AUC from time-zero to Day 29 after initiation of drug administration.

NA = not applicable

FIG. 24

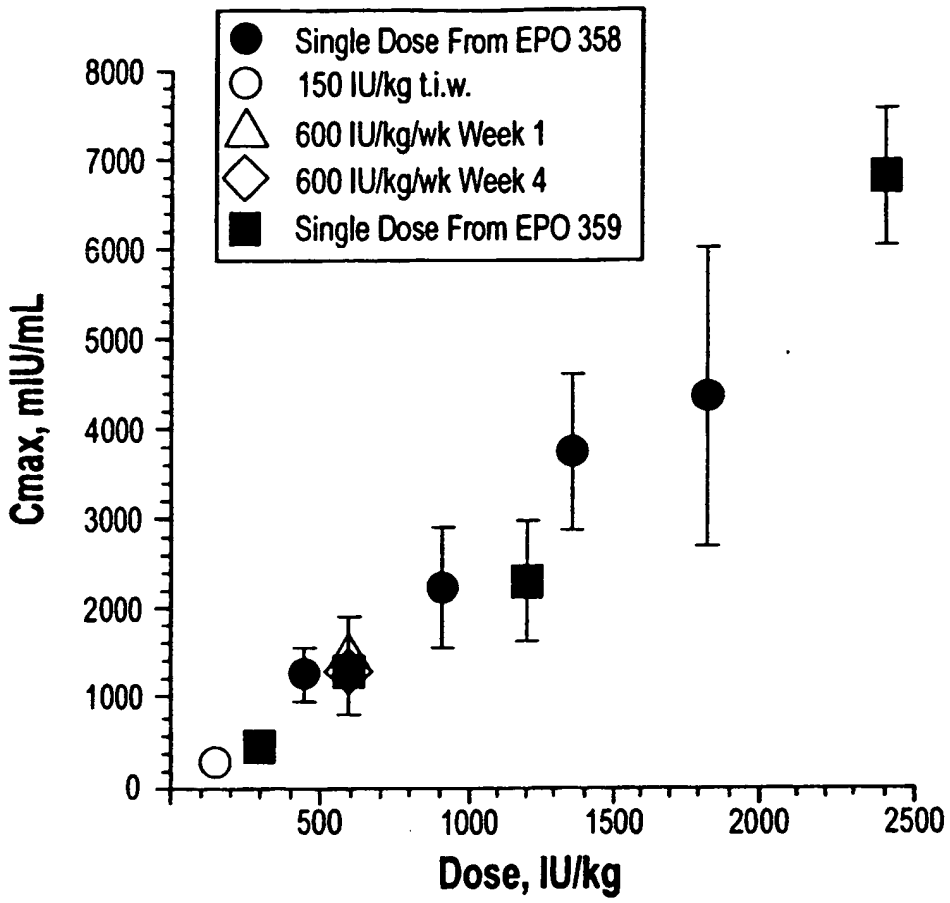

Single Dose From EPO 358
150 IU/kg t.i.w.
600 IU/kg/wk Week 1
600 IU/kg/wk Week 4
Single Dose From EPO 359
Cmax, mIU/mL
8000
7000
6000
5000
4000
3000
2000
1000
0
500
1000
1500
2000
2500
Dose, IU/kg

FIG. 25

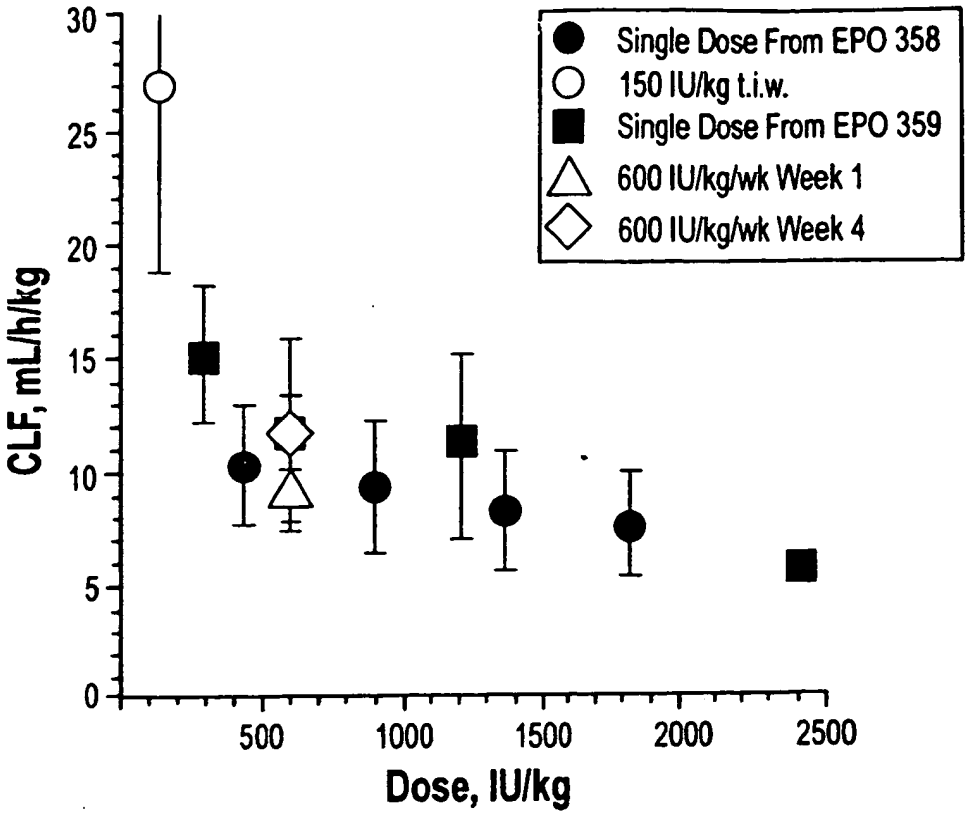

Single Dose From EPO 358
150 IU/kg t.i.w.
Single Dose From EPO 359
600 IU/kg/wk Week 1
600 IU/kg/wk Week 4
CLF, mL/h/kg
30
25
20
15
10
5
0
500
1000
1500
2000
2500
Dose, IU/kg

FIG. 26

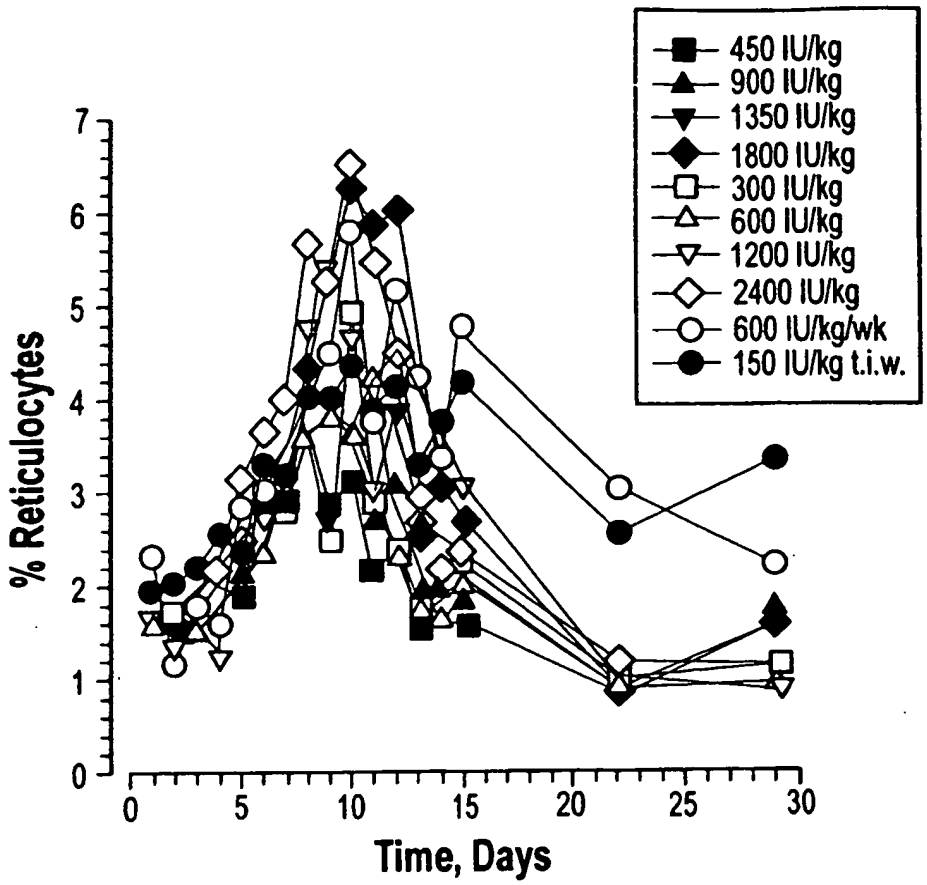

450 IU/kg
900 IU/kg
1350 IU/kg
1800 IU/kg
300 IU/kg
600 IU/kg
1200 IU/kg
2400 IU/kg
600 IU/kg/wk
150 IU/kg t.i.w.
% Reticulocytes
0
1
2
3
4
5
6
7
0
5
10
15
20
25
30
Time, Days

FIG. 27

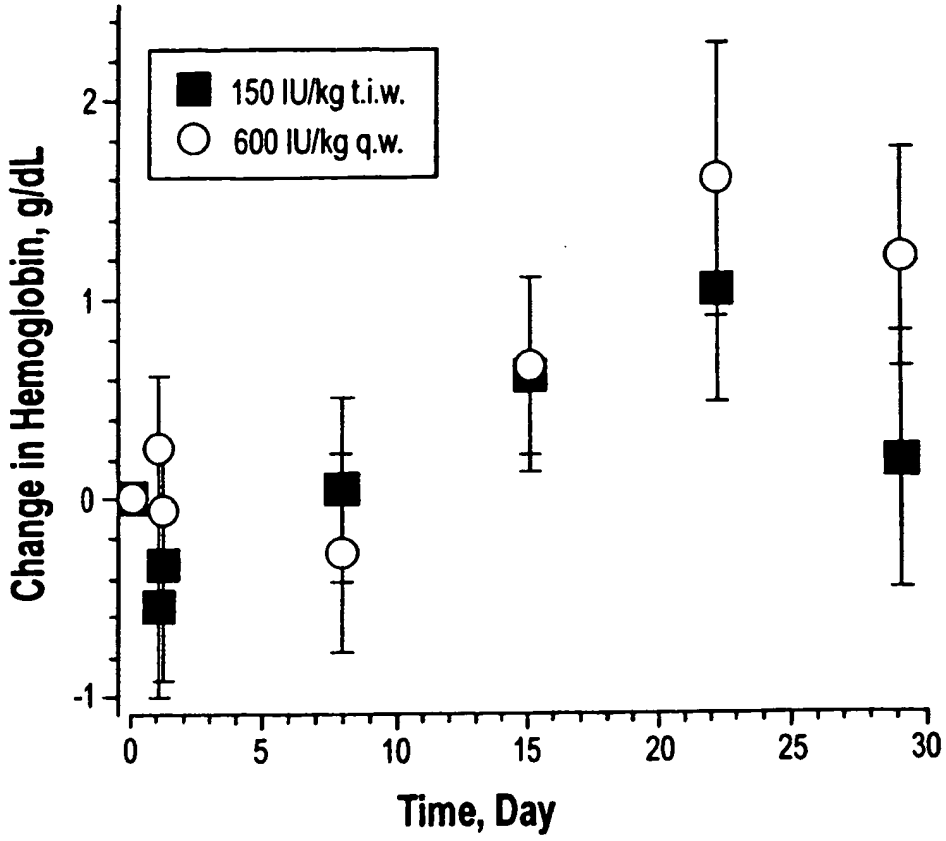

150 IU/kg t.i.w.
600 IU/kg q.w.
Change in Hemoglobin, g/dL
2
1
0
-1
0
5
10
15
20
25
30
Time, Day

FIG. 28

DEMOGRAPHIC DATA OF SUBJECTS IN CLINICAL STUDY EPO-PHI-370

TREATMENT	GENDER	WEIGHT (kg)	AGE (yr)	BASELINE HEMOGLOBIN (g/dL)
150 IU/kg t.i.w.	Male	74.3 ± 8.5	32.1 ± 5.5	14.7 ± 0.8
	(N = 9)	(63.2-85.0)	(26.0-41.0)	(13.5-15.6)
	Female	62.4 ± 10.3	34.6 ± 7.3	13.1 ± 0.9
	(N = 15)	(50.5-76.8)	(21.0-46.0)	(11.6-14.8)
	Overall	66.8 ± 11.1	33.7 ± 6.7	13.7 ± 1.1
	(N = 24)	(50.5-85.0)	(21.0-46.0)	(11.6-15.6)
40,000 IU q.w.	Male	72.4 ± 7.0	32.1 ± 8.6	14.6 ± 0.6
	(N = 14)	(61.8-84.5)	(19.0-44.0)	(13.5-15.6)
	Female	65.2 ± 7.8	35.1 ± 9.9	13.1 ± 0.7
	(N = 8)	(57.3-81.4)	(19.0-45.0)	(11.9-13.9)
	Overall	69.8 ± 8.0	33.2 ± 9.0	14.1 ± 1.0
	(N = 22)	(57.3-84.5)	(19.0-45.0)	(11.9-15.6)

FIG. 29

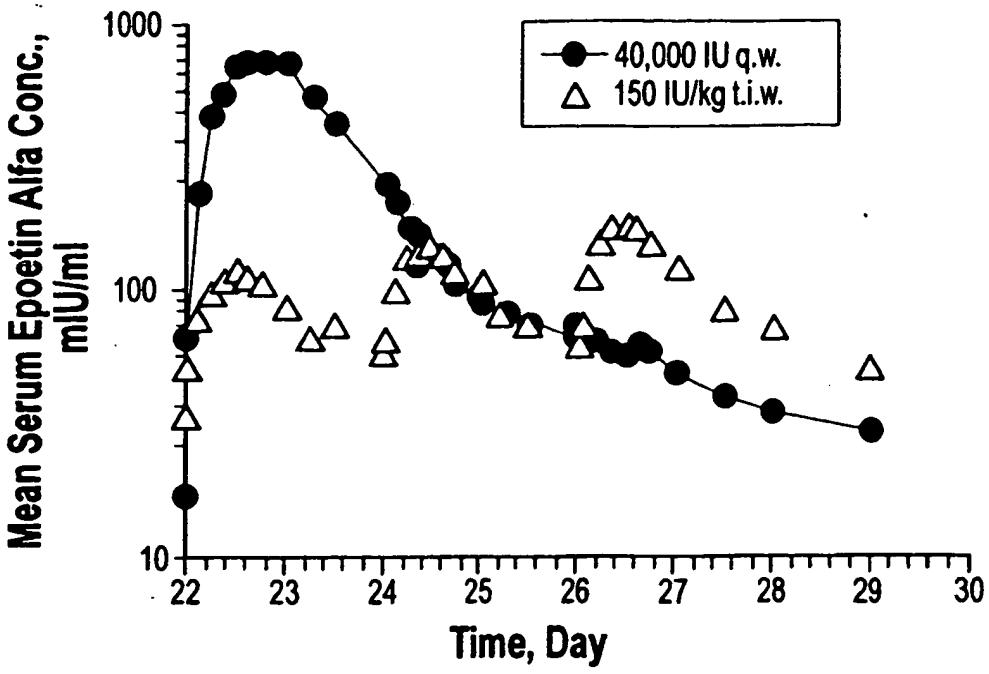

Mean Serum Epoetin Alfa Conc., mIU/ml
1000
100
10
22
23
24
25
26
27
28
29
30
Time, Day
40,000 IU q.w.
150 IU/kg t.i.w.

FIG. 30

MEAN ± SD (%CV) PHARMACOKINETIC PARAMETERS (PROTOCOL EPO-PHI-370)

Parameter	150 (IU/kg t.i.w.)	40,000 (IU q.w.)	RATIO[a]
C_{max} (mIU/mL)	191±100 (52.3%)	785±427 (54.4%)	4.11
C_{min} (mIU/mL)	39±18 (45.9%)	13±9 (73.1%)	0.33
t_{max} (h)	ND	18±5 (29.4%)	ND
AUC(0-168) (mIU•h/mL)	13446±4374 (32.5%)	30084±13516 (44.9%)	2.24
CL/F (mL/h/kg)	37.1±12.3 (33.1)	23.2±10.8 (46.5)	0.63

[a] Parameter ratio of the mean values, 40,000 IU q.w./150 IU/kg t.i.w.
ND = Not Determined

FIG. 31

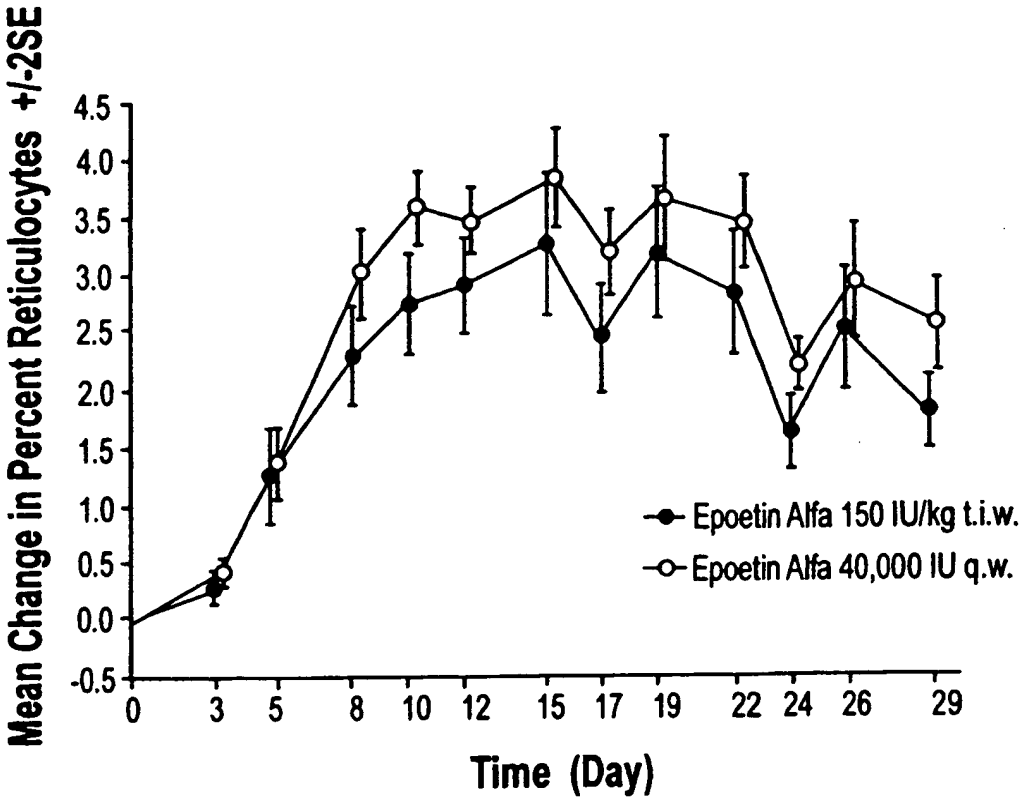

Mean Change in Percent Reticulocytes +/-2SE
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
0
3
5
8
10
12
15
17
19
22
24
26
29
Time (Day)
Epoetin Alfa 150 IU/kg t.i.w.
Epoetin Alfa 40,000 IU q.w.

FIG. 32

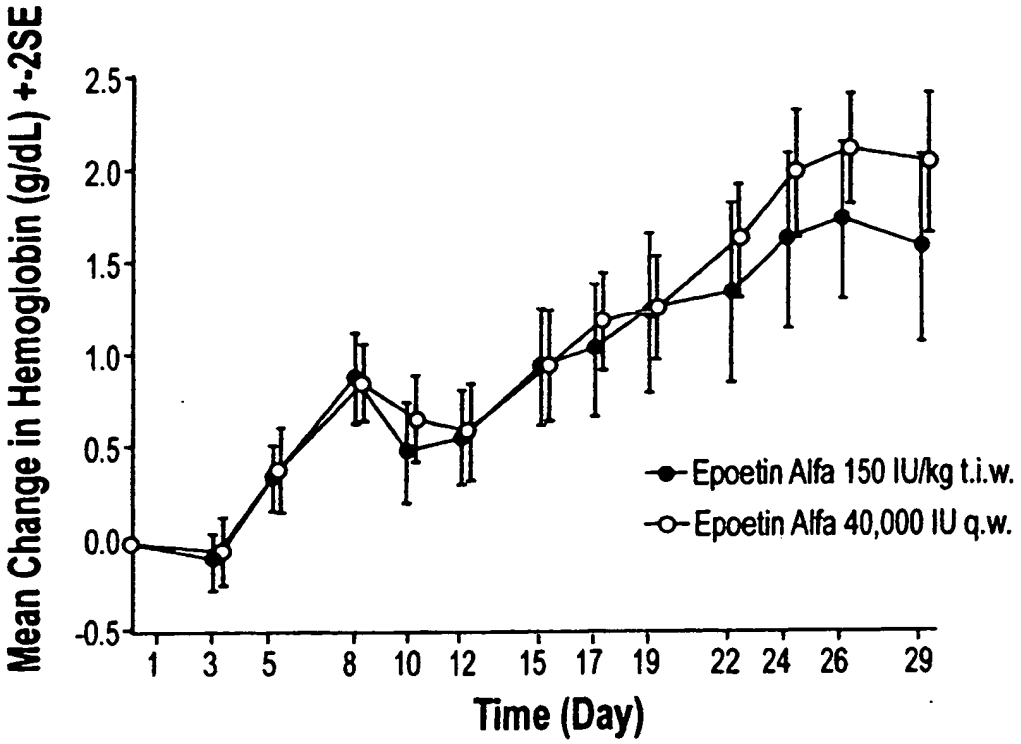

Mean Change in Hemoglobin (g/dL) +-2SE
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1
3
5
8
10
12
15
17
19
22
24
26
29
Time (Day)
Epoetin Alfa 150 IU/kg t.i.w.
Epoetin Alfa 40,000 IU q.w.

FIG. 33

Mean ± SD (%CV) Pharmacodynamic Parameters Corrected for Baseline Value (Protocol EPO-PHI-370)

Treatment Group	Auc(RETI)[a] (%·d)	AUC(HEMO)[b] (g·d/dL)	AUC(RBC)[c] ($x10^{12}$cells·d/L)
150 IU/kg t.i.w.			
Male	56.8 ± 21.5	26.4 ± 11.6	12.0 ± 4.6
(N = 9)	(37.8%)	(43.7%)	(37.8%)
Female	66.6 ± 19.8	28.7 ± 18.6	12.3 ± 5.5
(N = 15)	(29.7%)	(64.9%)	(44.9%)
All Subjects	62.9 ± 20.5[d]	27.9 ± 16.1	12.2 ± 5.1
(N = 24)	(32.7%)	(57.8%)	(41.7%)
40,000 IU q.w.			
Male	75.5 ± 9.8	35.3 ± 11.2	14.1 ± 4.0
(N = 14)	(12.9%)	(31.8%)	(28.6%)
Female	80.3 ± 10.1	23.5 ± 11.5	10.9 ± 3.3
(N = 8)	(12.5%)	(48.8%)	(30.6%)
All Subjects	77.2 ± 9.9[d]	31.0 ± 12.5	12.9 ± 4.0
(N = 22)	(12.8%)	(40.3%)	(31.1%)
Ratio for All Subjects[e]	1.23	1.11	1.06
All Females[f]	71.3 ± 18.0	26.9 ± 16.4	11.8 ± 4.9
(N = 23)	(25.3%)	(61.0%)	(41.0%)
All Males[g]	68.2 ± 17.7	31.8 ± 12.0	13.3 ± 4.3
(N = 23)	(25.9%)	(37.6%)	(32.0%)

FIG. 34

Mean ± SD Demographic Data of Subjects in Clinical Study EPO-PHI-373

Treatment	Gender	Weight (kg)	Age (yr)	Baseline Hemoglobin (g/dL)
150 IU/kg t.i.w.	Male (N = 9)	72.1 ± 8.2 (64.5-90.5)	26.4 ± 5.2 (21.0-37.0)	14.0 ±0.4 (13.2-14.8)
	Female (N = 8)	61.0 ± 4.8 (53.3-66.4)	24.3 ± 3.5 (20.0-29.0)	12.8 ± 0.7 (11.7-13.8)
	Overall (N = 17)	66.9 ± 8.7 (53.3-90.5)	25.4 ± 4.5 (20.0-37.0)	13.4 ± 0.8 (11.7-14.8)
40,000 IU q.w.	Male (N = 9)	77.0 ± 12.8 (67.3-106)	29.4 ± 5.5 (19.0-36.0)	13.9 ± 0.5 (13.3-14.6)
	Female (N = 8)	63.7 ± 8.8 (51.0-78.0)	26.5 ± 7.5 (18.0-41.0)	13.0 ± 0.8 (12.2-14.2)
	Overall (N = 17)	70.7 ± 12.7 (51.0-106)	28.1 ± 6.5 (18.0-41.0)	13.5 ± 0.8 (12.2-14.6)

FIG. 35

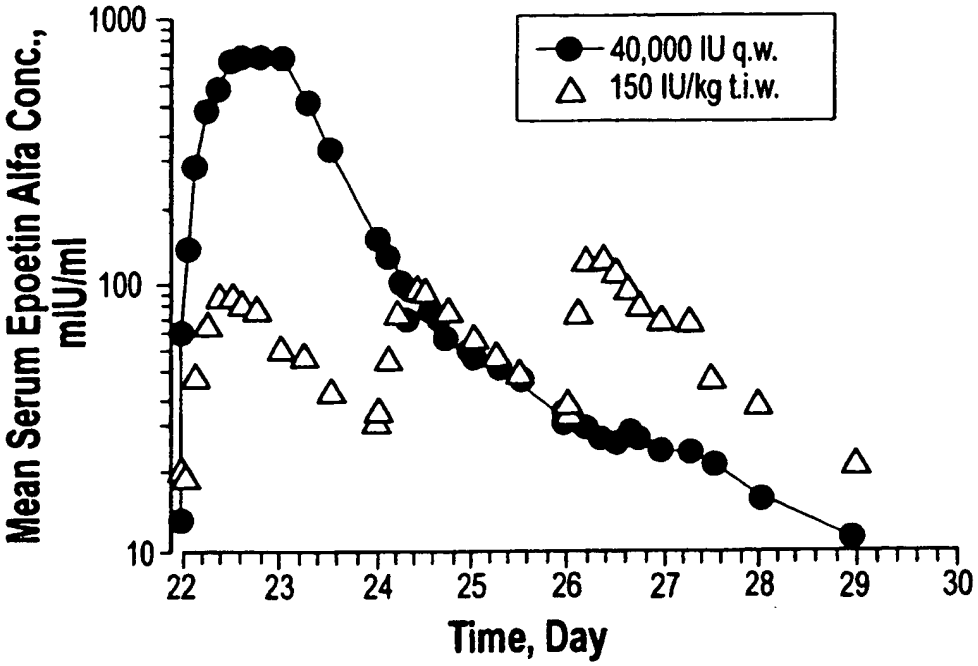

1000
100
10
Mean Serum Epoetin Alfa Conc., mIU/ml
40,000 IU q.w.
150 IU/kg t.i.w.
22
23
24
25
26
27
28
29
30
Time, Day

FIG. 36

Mean ± SD Pharmacokinetic Parameters (Protocol EPO-PHI-373)

Parameter	150 (IU/kg t.i.w.)	40,000 (IU q.w.)	Ratio[a]
C_{max} (mIU/mL)	143 ± 54 (37.8%)	861 ± 445 (51.7%)	6.02(13.2-14.8)
C_{min} (mIU/mL)	18 ± 9 (50.7%)	3.8 ± 4.3 (114%)	0.21
t_{max} (h)	ND	16 ± 8 (45.6%)	ND
AUC(0-168) (mIU·h/mL)	8587 ± 1521 (17.7%)	25747 ± 9062 (35.2%)	3.00
CL/F (mL/h/kg)	51.4 ± 10.1 (18.7%)	24.7 ± 7.2 (29.1%)	0.46

[a] Parameter ratio of the mean values, 40,000 IU q.w./150 IU/kg t.i.w.

ND = not determined

FIG. 37

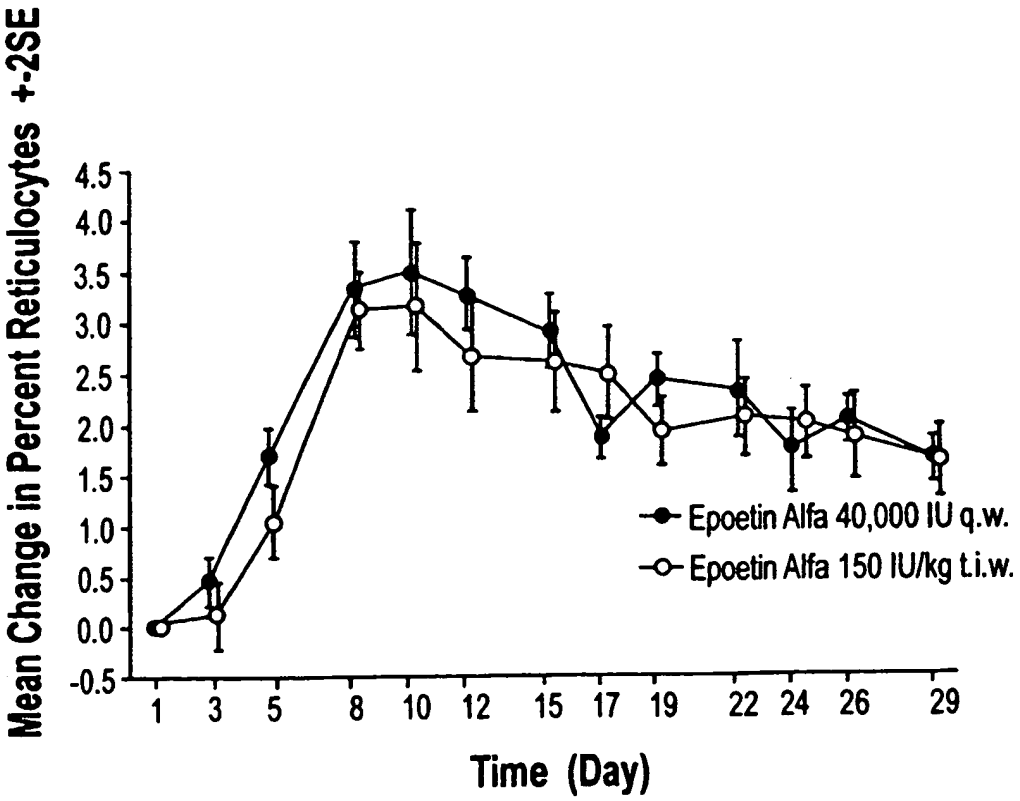

Mean Change in Percent Reticulocytes +-2SE
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1
3
5
8
10
12
15
17
19
22
24
26
29
Time (Day)
Epoetin Alfa 40,000 IU q.w.
Epoetin Alfa 150 IU/kg t.i.w.

FIG. 38

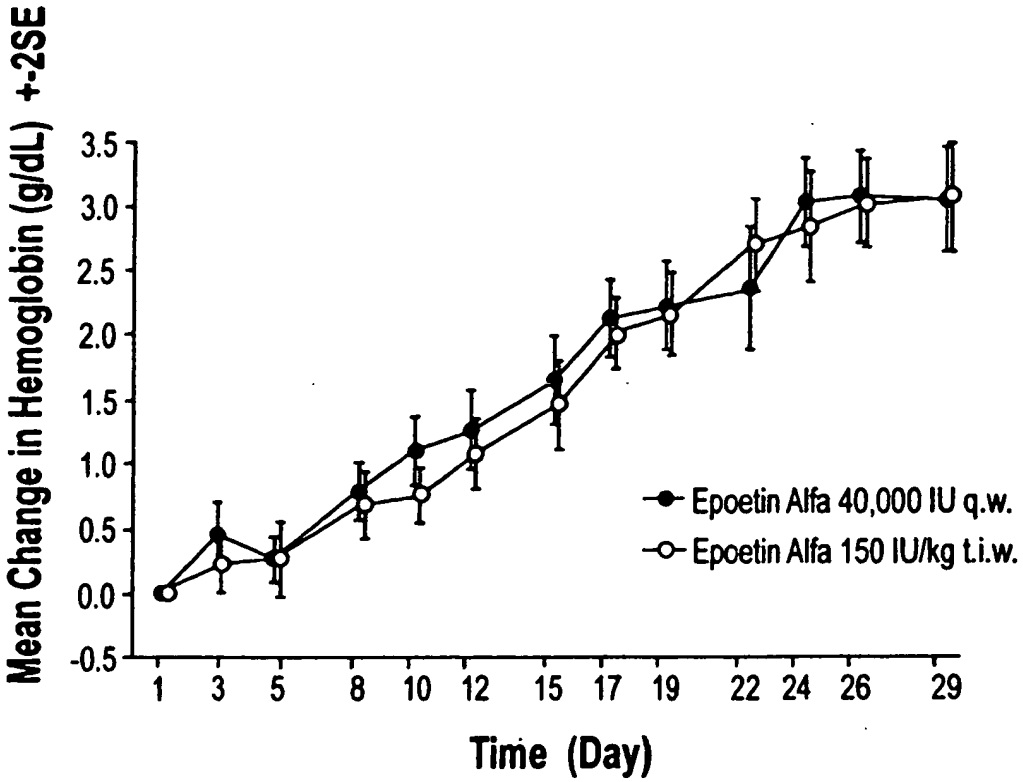

Mean Change in Hemoglobin (g/dL) +-2SE
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1
3
5
8
10
12
15
17
19
22
24
26
29
Time (Day)
Epoetin Alfa 40,000 IU q.w.
Epoetin Alfa 150 IU/kg t.i.w.

FIG. 39

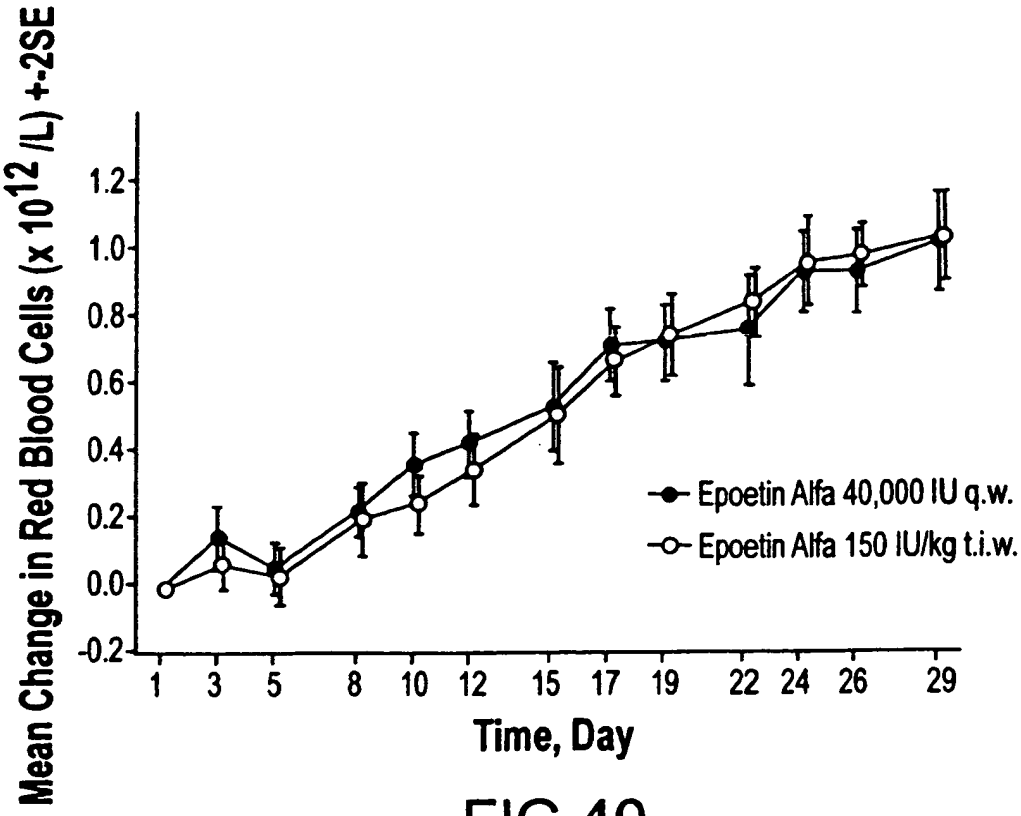

Mean Change in Red Blood Cells (x 10^12 /L) +-2SE
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
1
3
5
8
10
12
15
17
19
22
24
26
29
Time, Day
Epoetin Alfa 40,000 IU q.w.
Epoetin Alfa 150 IU/kg t.i.w.

FIG.40

Mean ± SD (%CV) Pharmacodynamic Parameters Corrected for Baseline Value (Protocol EPO-PHI-373)

Treatment Group	Auc(RETI)[a] (%·d)	AUC(HEMO)[b] (g·d/dL)	AUC(RBC)[c] ($x10^{12}$·d/L)
150 IU/kg t.i.w.			
Male	55.1 ± 14.4	40.4± 13.0	13.4± 3.9
(N = 9)	(23.1%)	(32.3%)	(29.3%)
Female	59.6 ± 21.3	51.1 ± 10.9	16.4 ± 4.4
(N = 8)	(35.7%)	(21.4%)	(26.7%)
All Subjects	57.2 ± 17.5	45.4 ± 12.9	14.8 ± 4.3
(N = 17)	(30.6%)	(28.5%)	(29.0%)
40,000 IU q.w.			
Male	58.8 ± 10.4	43.5 ± 11.6	13.6 ± 4.3
(N = 9)	(17.7%)	(26.6%)	(31.3%)
Female	68.4 ± 14.4	52.4 ± 15.0	16.9 ± 4.3
(N = 8)	(21.1%)	(28.6%)	(25.5%)
All Subjects	63.3 ± 13.0	47.7 ± 13.6	15.1 ± 4.5
(N = 17)	(20.5%)	(28.6%)	(29.5%)
Ratio for All Subjects[d]	1.11	1.05	1.02
All Females[e]	64.0 ± 18.1	51.7 ± 12.7g	16.6 ± 4.2g
(N = 16)	(28.3%)	(24.5%)	(25.3%)
All Males[f]	57.0 ± 12.3	41.9 ± 12.0g	13.5 ± 4.0g
(N = 18)	(21.6%)	(28.7%)	(29.5%)

FIG. 41

Mean = SD (%CV) Pharmacokinetic Parameters (Clinical Studies EPO-PHI-358, EPO-PHI-359, EPO-PHI-370, and EPO-PHI-373)

Study	Dose	C_{max} (mIU/mL)	t_{max} (h)	AUC[a] (mIU·h/mL)	CL/F (mL/h/kg)	$t_{1/2}$ (h)
Single Subcutaneous Dose Administration						
EPO359	300 IU/kg	429 ± 86 (20.0%)	22.8 ± 8.1 (36.5%)	20056 ± 4138 (20.6%)	15.5 ± 3.1 (20.2%)	68.2 ± 52.2 (76.6%)
EPO358	450 IU/kg	1263 ± 290 (23.0%)	15.6 ± 5.8 (37.0%)	45498 ± 12342 (27.1%)	10.4 ± 2.6 (24.9%)	24.2 ± 3.2 (13.2%)
EPO359	600 IU/kg	1263 ± 486 (38.5%)	27.6 ± 9.1 (33.0%)	55475 ± 16384 (29.5%)	11.8 ± 4.2 (35.5%)	29.3 ± 9.4 (32.0%)
EPO358	900 IU/kg	2235 ± 599 (26.8%)	22.2 ± 12.7 (57.0%)	103154 ± 28024 (27.2%)	9.36 ± 2.97 (31.7%)	36.0 ± 13.5 (37.3%)
EPO359	1200 IU/kg	2256 ± 710 (31.4%)	26.4 ± 7.8 (29.4%)	119932 ± 44217 (36.9%)	11.2 ± 4.2 (37.7%)	78.5 ± 95.4 (122%)
EPO358	1350 IU/kg	3755 ± 879 (23.4%)	23.4 ± 8.8 (37.8%)	174193 ± 41417 (23.8%)	8.23 ± 2.57 (31.3%)	33.4 ± 2.4 (7.2%)
EPO358	1800 IU/kg	4370 ± 1673 (38.3%)	28.8 ± 7.8 (27.2%)	258600 ± 101175 (39.1%)	7.64 ± 2.22 (29.1%)	32.4 ± 8.4 (25.9%)
EPO359	2400 IU/kg	6819 ± 764 (11.2%)	25.2 ± 6.2 (24.7%)	429441 ± 32139 (7.5%)	5.61 ± 0.44 (7.8%)	43.6 ± 25.9 (59.5%)
Multiple Subcutaneous Dose Administration						
EPO358 Wk 4	150 IU/kg t.i.w.	252 ± 71 (28.0%)	NA	16582 ± 4256 (25.7%)	28.7 ± 7.8 (27.1%)	25.9 ± 7.1 (27.2%)
EPO359 Wk 1	600 IU/kg q.w.	1502 ± 384 (25.6%)	21.6 ± 6.1 (28.5%)	63439 ± 10893 (17.2%)	9.70 ± 1.8 (18.1%)	28.3 ± 7.5 (26.3%)
EPO359 Wk 4	600 IU/kg q.w.	1278 ± 213 (16.6%)	24.0 ± 8.7 (36.4%)	50725 ± 6774 (13.4%)	12.0 ± 1.6 (13.2%)	28.1 ± 7.0 (24.9%)

FIG. 42

Applicant:	The R.W. Johnson Pharmaceutical Research Institute					
Drug:	Epoetin Alfa Once Weekly Dosing					
NDA No.:	Insert NDA No.					
Study	Dose	C_{max} (mIU/mL)	t_{max} (h)	AUC[a] (mIU·h/mL)	CL/F (mL/h/kg)	$t_{1/2}$ (h)
Single Subcutaneous Dose Administration						
EPO370 Wk 4	150 IU/kg t.i.w.	191 ± 100 (52.3%)	NA	13446 ± 4374 (32.5%)	37.1 ± 12.3 (33.1%)	31.8 ± 13.4 (42.1%)
EPO370 Wk 4	40,000 IU q.w.	785 ± 427 (54.4%0)	18 ± 5 (29.4%)	30084 ± 13516 (44.9%)	23.2 ± 10.8 (46.5%)	39.3 ± 7.1 (18.1%)
EPO373 Wk 4	150 IU/kg t.i.w.	143 ± 54 (37.8%)	NA	8587 ± 1521 (17.7%)	54.1 ± 10.1 (18.7%)	19.4 ± 8.1 (41.5%)
EPO373 Wk 4	40,000 IU q.w.	861 ± 445 (51.7%)	16 ± 8 (45.6%)	25.747 ± 9062 (35.2%)	24.7 ± 7.2 (29.1%)	15.0 ± 6.1 (40.9%)

[a] AUC(0-168) during a dose week for multiple dose regimens and AUC(0-672) during the 4-wk of study period for single doses.

NA = Not applicable

FIG. 42

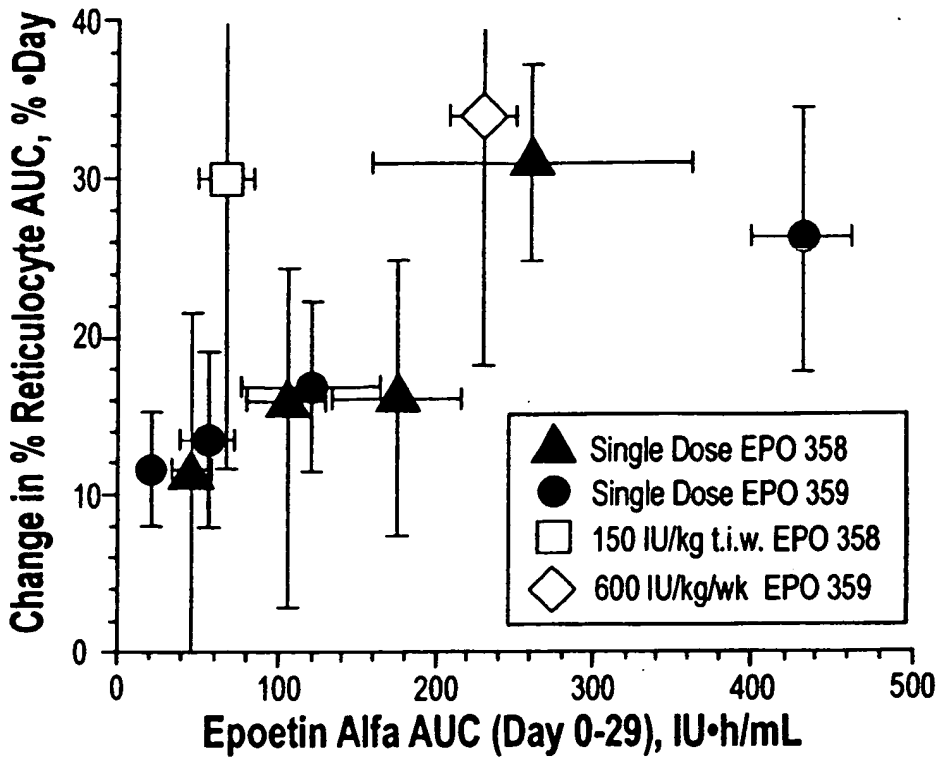

Change in % Reticulocyte AUC, % •Day
Epoetin Alfa AUC (Day 0-29), IU•h/mL
0
10
20
30
40
0
100
200
300
400
500
Single Dose EPO 358
Single Dose EPO 359
150 IU/kg t.i.w. EPO 358
600 IU/kg/wk EPO 359

FIG. 43

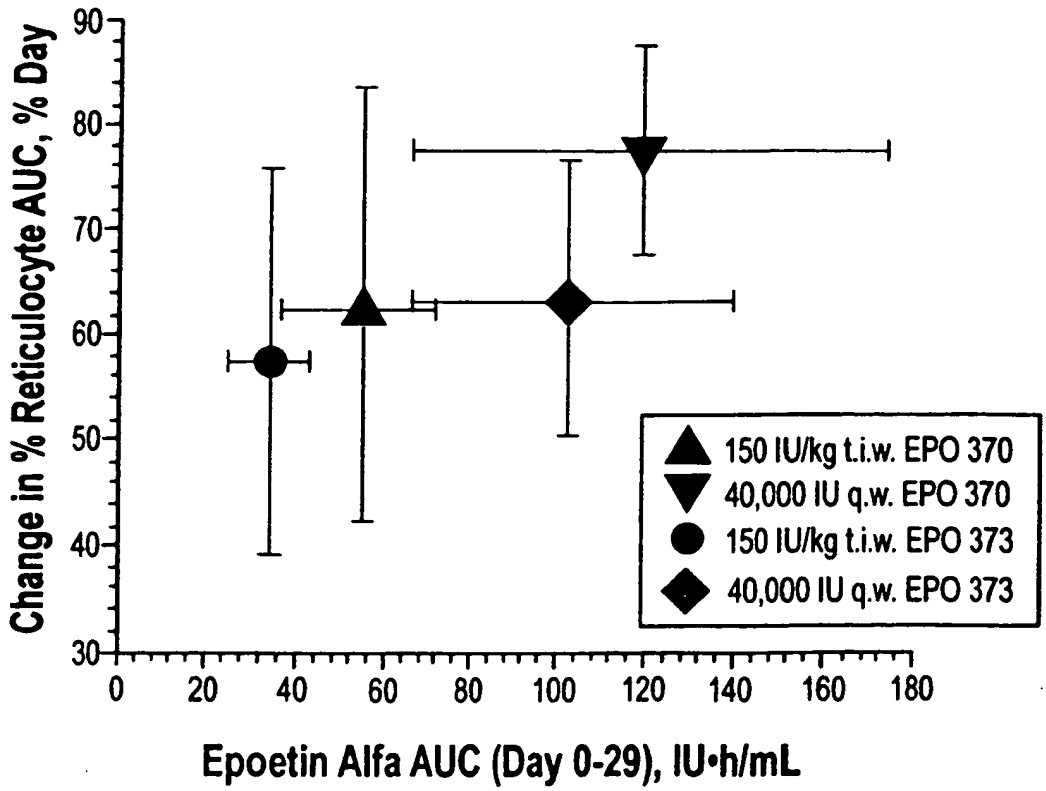

Change in % Reticulocyte AUC, % Day
90
80
70
60
50
40
30
0
20
40
60
80
100
120
140
160
180
Epoetin Alfa AUC (Day 0-29), IU•h/mL
150 IU/kg t.i.w. EPO 370
40,000 IU q.w. EPO 370
150 IU/kg t.i.w. EPO 373
40,000 IU q.w. EPO 373

FIG. 44

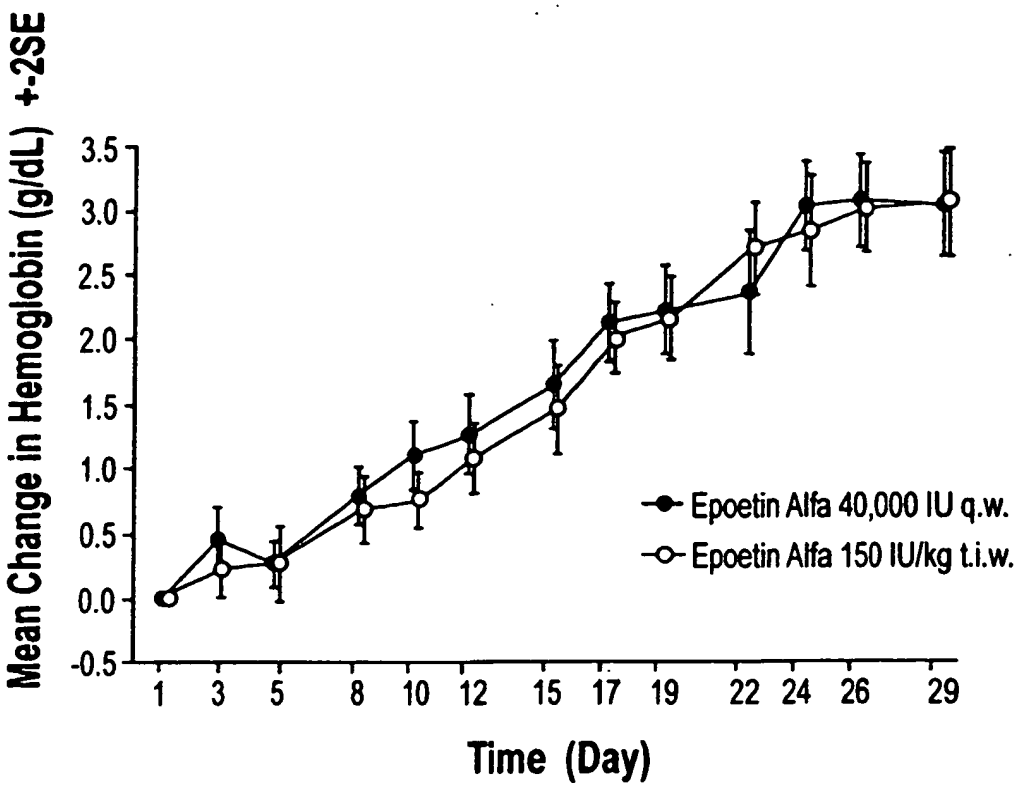

Mean Change in Hemoglobin (g/dL) +-2SE
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1
3
5
8
10
12
15
17
19
22
24
26
29
Time (Day)
Epoetin Alfa 40,000 IU q.w.
Epoetin Alfa 150 IU/kg t.i.w.

FIG. 45

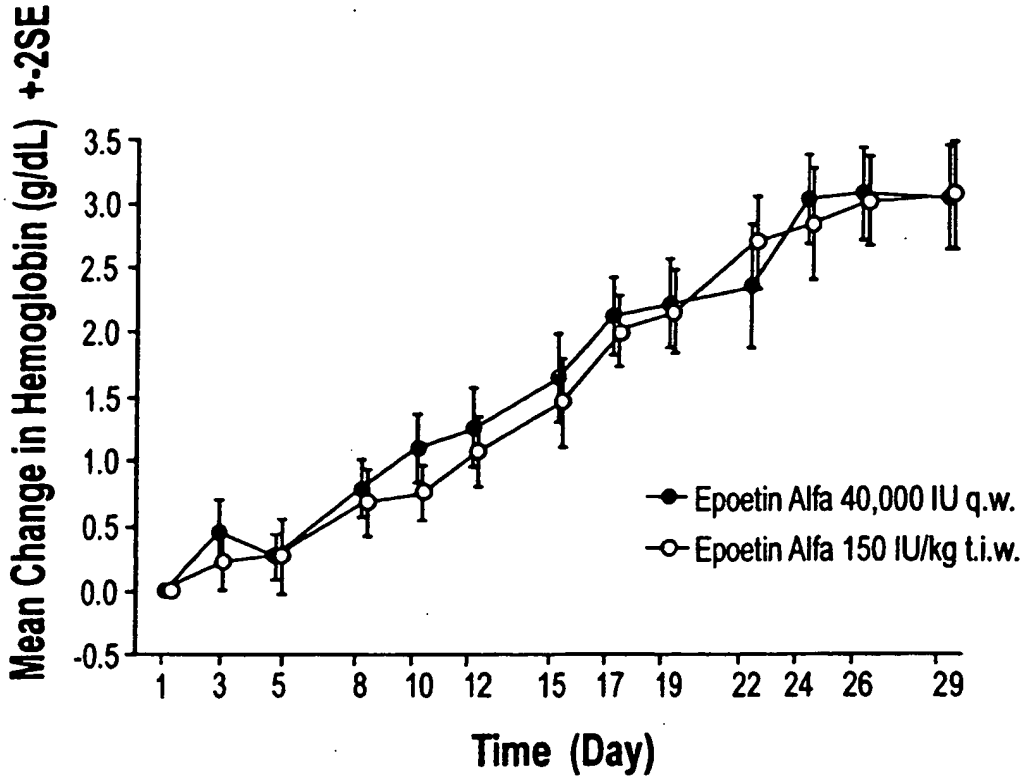

Mean Change in Hemoglobin (g/dL) +-2SE
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1
3
5
8
10
12
15
17
19
22
24
26
29
Time (Day)
Epoetin Alfa 40,000 IU q.w.
Epoetin Alfa 150 IU/kg t.i.w.

FIG. 46

Demographic and Baseline Characteristics (All Subjects in Protocol EPO-PHI-373)

Characteristic	Epoetin Alfa 150 IU/kg t.i.w. (N=18)	Epoetin Alfa 40,000 IU q.w. (N=18)	Total (N=36)
Sex			
Male	9 (50%)	9 (50%)	18 (50%)
Female	9 (50%)	9 (50%)	18 (50%)
Age (years)			
Mean (SD)	25.3 (4.34)	27.7 (6.48)	26.5 (5.57)
Median	24	27.5	25.0
Range	20.0-37.0	18.0-41.0	18.0-41.0
Weight (kg)			
Mean (SD)	66.8 (8.47)	70.3 (12.51)	68.6 (10.67)
Median	66.0	69.0	67.3
Range	53.3-90.5	51.0-105.5	51.0-105.5
Height (cm)			
Mean (SD)	171.9 (6.94)	170.9 (8.86)	171.4 (7.86)
Median	172.8	169.5	171.8
Range	160.5-191.0	160.5-191.0	160.5-191.0
Race			
White	17 (94%)	15 (83%)	32 (89%)
Black	1 (6%)	2 (11%)	3 (8%)
Other	0 (0%)	1 (6%)	1 (3%)

FIG. 47

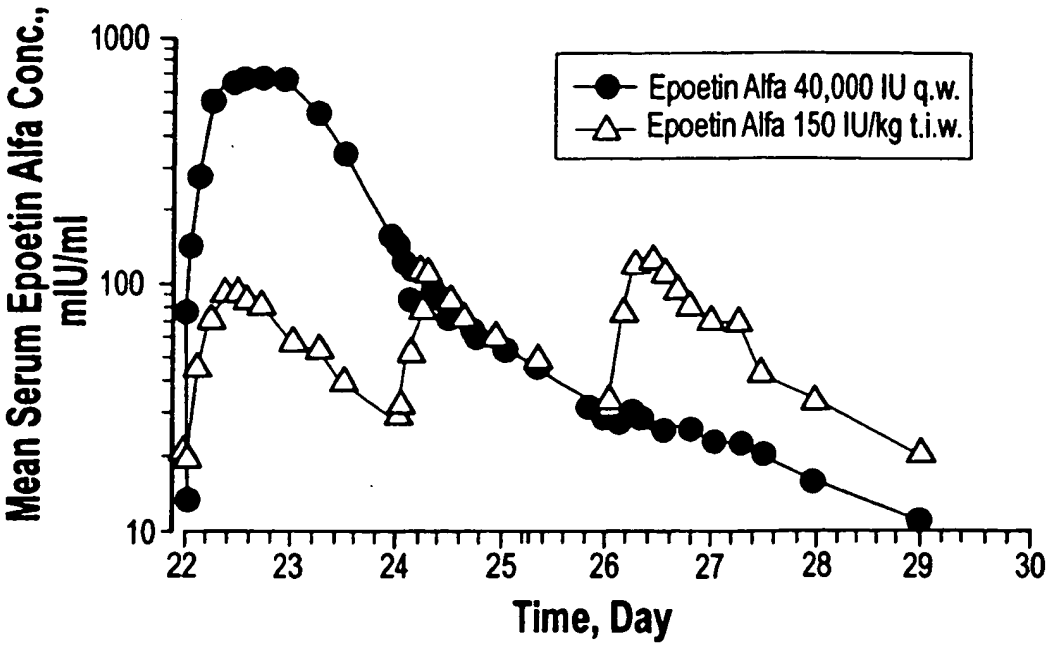

Mean Serum Epoetin Alfa Conc., mIU/ml
1000
100
10
22
23
24
25
26
27
28
29
30
Time, Day
Epoetin Alfa 40,000 IU q.w.
Epoetin Alfa 150 IU/kg t.i.w.

FIG. 48

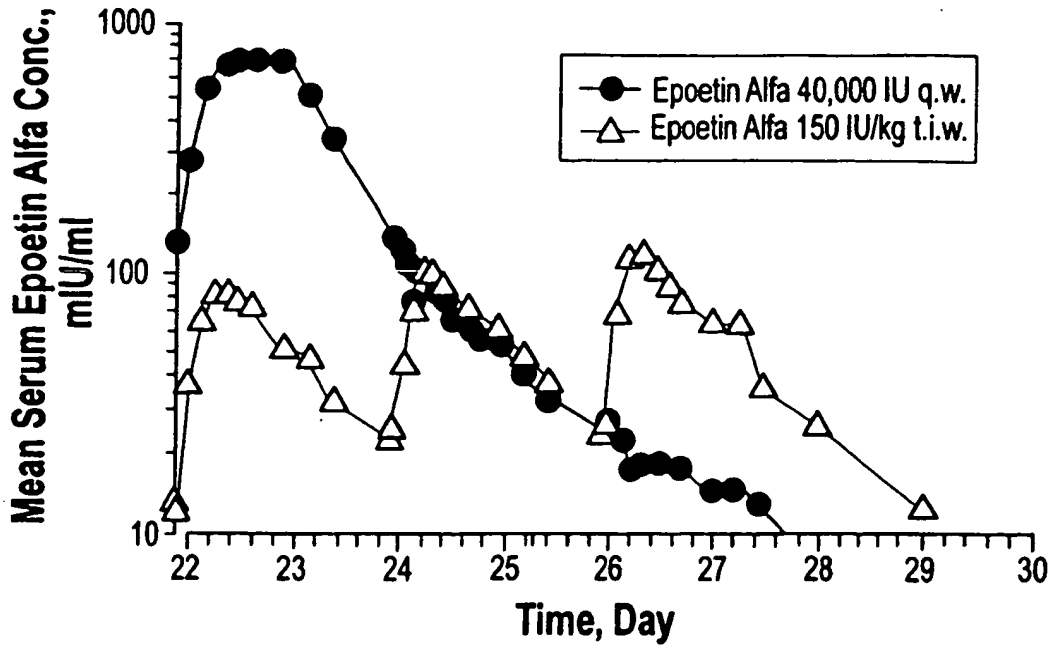

Mean Serum Epoetin Alfa Conc., mIU/ml
1000
100
10
22
23
24
25
26
27
28
29
30
Time, Day
Epoetin Alfa 40,000 IU q.w.
Epoetin Alfa 150 IU/kg t.i.w.

FIG. 49

SELECTED MEAN (SD) [%CV] PHARMACOKINETIC PARAMETERS (SUBJECTS IN THE EFFICACY POPULATION IN PROTOCOL EPO-PHI-373)

	150 IU/kg t.i.w. (n=17)		40,000 IU q.w. (n-17)		
Parameter	Mean (SD)	[%CV]	Mean (SD)	[%CV]	Ratio[a]
C_{max} (mIU/mL)	143 (54)	[37.8%]	861 (445)	[51.7%]	6.02
C_{min} (mIU/mL)	18 (9)	[50.7%]	3.8 (4.3)	[114%]	0.21
t_{max} (h)	ND		16 (8)	[45.6%]	ND
$AUC_{(0\text{-}168)}$ (mIU•h/mL)	8587 (1521)	[17.7%]	25747 (9062)	[35.2%]	3.00
CL/F (mL/h/kg)	54.1 (10.1)	[18.7%]	24.7 (7.2)	[29.1%]	0.46

[a] Parameter ratio of the mean values, 40,000 IU q.w./150 IU/kg t.i.w.
ND = Not determined

FIG. 50

MEAN (SD) CHANGE FROM BASELINE IN PERCENT RETICULOCYTES (SUBJECTS IN THE EFFICACY POPULATION-PROTOCOL EPO-PHI-373)

	Epoetin Alfa 150 IU/kg t.i.w.			Epoetin Alfa 40,000 IU/kg q.w.		
	N	Mean (SD)	Range	N	Mean (SD)	Range
Baseline	17	1.5 (0.59)	0.9-2.9	17	1.4 (0.45)	0.8-2.5
Change from Baseline to Day						
Day 3	17	1.1 (0.68)	-2.0-1.3	17	0.5 (0.51)	-0.3-1.8
Day 5	17	1.1 (0.76)	-1.0-2.2	17	1.7 (0.56)	0.5-2.7
Day 8	17	3.1 (0.77)	1.9-4.3	17	3.3 (0.97)	2.0-5.3
Day 10	17	3.2 (1.30)	1.8-5.5	17	3.5 (1.26)	1.4-6.8
Day 12	17	2.7 (1.12)	0.3-5.4	17	3.3 (0.74)	2.0-5.5
Day 15	17	2.6 (1.02)	1.0-4.8	17	2.9 (0.76)	1.6-4.9
Day 17	17	2.5 (0.94)	-1.7-5.4	17	1.9 (0.42)	1.3-2.7
Day 19	17	1.9 (0.74)	-0.0-3.4	17	2.4 (0.53)	1.7-3.6
Day 22	17	2.1 (0.78)	-0.1-2.9	17	2.4 (1.00)	0.7-4.5
Day 24	17	2.0 (0.73)	0.3-3.1	16	1.7 (0.82)	-0.0-3.2
Day 26	17	1.9 (0.90)	-0.3-4.0	17	2.1 (0.47)	1.0-2.7
Day 29	17	1.7 (0.74)	-0.3-3.2	17	1.7 (0.46)	1.0-2.7
Last Visit	17	1.7 (0.74)	-0.3-3.2	17	1.7 (0.46)	1.0-2.7

FIG. 51

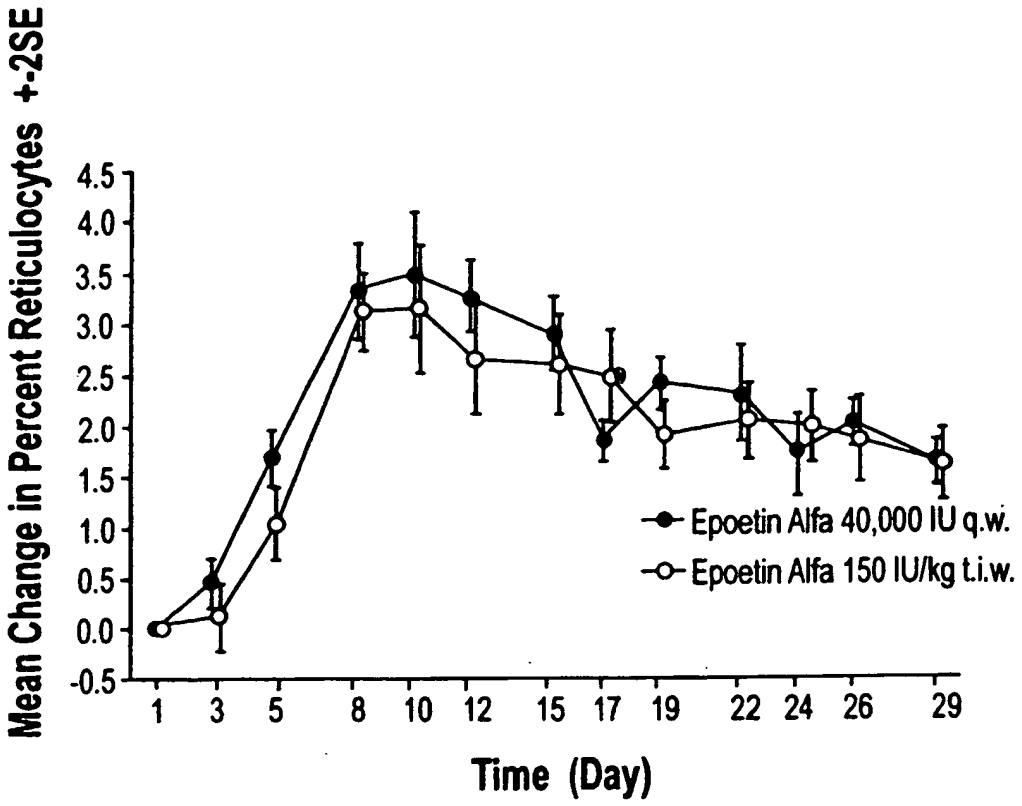

Mean Change in Percent Reticulocytes +-2SE
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1
3
5
8
10
12
15
17
19
22
24
26
29
Time (Day)
Epoetin Alfa 40,000 IU q.w.
Epoetin Alfa 150 IU/kg t.i.w.

FIG. 52

MEAN (SD) CHANGE FROM BASELINE IN HEMOGLOBIN (g/dL) (SUBJECTS IN THE EFFICACY POPULATION-PROTOCOL EPO-PHI-373)

	Epoetin Alfa 150 IU/kg t.i.w.			Epoetin Alfa 40,000 IU/kg q.w.		
	N	Mean (SD)	Range	N	Mean (SD)	Range
Baseline	17	13.4 (0.81)	11.7-14.8	17	13.5 (0.79)	12.2-14.6
Change from Baseline to Day						
Day 3	17	0.2 (0.45)	-0.5-1.1	17	0.5 (0.52)	-0.5-1.5
Day 5	17	1.3 (0.63)	-0.6-1.8	17	0.3 (0.37)	-0.4-0.8
Day 8	17	0.7 (0.54)	-0.4-1.8	17	0.8 (0.47)	1.0-1.7
Day 10	17	0.8 (0.45)	-0.2-1.5	17	1.1 (0.56)	0.2-2.4
Day 12	17	1.1 (0.57)	0.4-2.2	17	1.3 (0.65)	0.1-2.4
Day 15	17	1.5 (0.72)	0.2-2.4	17	1.7 (0.73)	0.2-2.7
Day 17	17	2.0 (0.57)	1.0-3.0	17	2.1 (0.62)	1.0-3.2
Day 19	17	2.2 (0.68)	1.2-3.2	17	2.2 (0.69)	1.2-3.2
Day 22	17	2.7 (0.74)	1.4-3.9	17	2.4 (1.00)	0.7-4.7
Day 24	17	2.9 (0.90)	0.7-4.2	16	3.0 (0.70)	1.6-4.0
Day 26	17	3.0 (0.69)	1.8-4.3	17	3.1 (0.74)	1.9-4.4
Day 29	17	3.1 (0.86)	1.4-4.5	17	3.1 (0.84)	1.8-4.6
Last Visit	17	3.1 (0.86)	1.4-4.5	17	3.1 (0.84)	1.8-4.6

FIG. 53

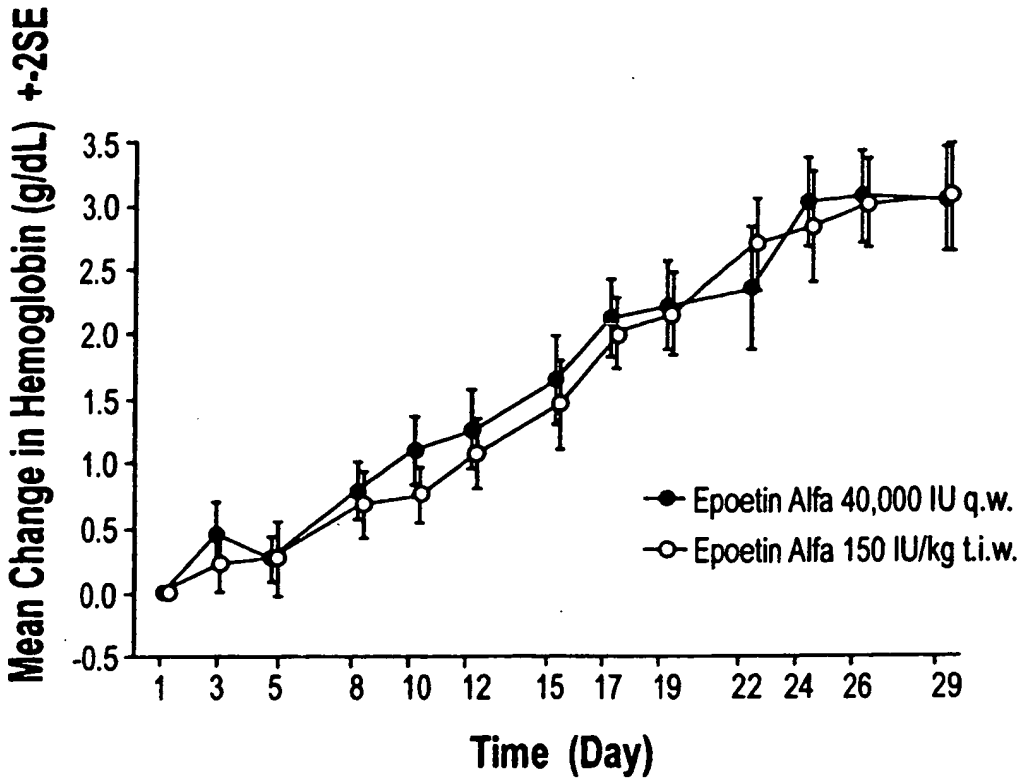

Mean Change in Hemoglobin (g/dL) +-2SE
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1
3
5
8
10
12
15
17
19
22
24
26
29
Time (Day)
Epoetin Alfa 40,000 IU q.w.
Epoetin Alfa 150 IU/kg t.i.w.

FIG. 54

MEAN (SD) CHANGE FROM BASELINE IN RED BLOOD CELLS ($x10^{12}/L$) (SUBJECTS IN THE EFFICACY POPULATION-PROTOCOL EPO-PHI-373)

	Epoetin Alfa 150 IU/kg t.i.w.			Epoetin Alfa 40,000 IU/kg q.w.		
	N	Mean (SD)	Range	N	Mean (SD)	Range
Baseline	17	4.4 (0.30)	3.8-5.1	17	4.4 (0.26)	4.0-4.8
Change from Baseline to Day						
Day 3	17	0.1 (0.16)	-0.2-0.4	17	0.2 (0.19)	-0.2-0.5
Day 5	17	0.0 (0.18)	-0.2-0.4	17	0.1 (0.15)	-0.2-0.3
Day 8	17	0.2 (0.21)	-0.2-0.8	17	0.2 (0.14)	0.0-0.5
Day 10	17	0.2 (0.17)	-0.1-0.5	17	0.4 (0.18)	0.1-0.8
Day 12	17	0.3 (0.21)	-0.1-0.7	17	0.4 (0.20)	-0.0-0.7
Day 15	17	0.5 (0.29)	0.0-0.9	17	0.5 (0.27)	-0.1-0.9
Day 17	17	0.7 (0.20)	0.3-1.0	17	0.7 (0.21)	0.4-1.1
Day 19	17	0.7 (0.24)	0.3-1.1	17	0.7 (0.22)	0.3-1.1
Day 22	17	0.8 (0.20)	0.5-1.2	17	0.8 (0.34)	0.2-1.4
Day 24	17	1.0 (0.28)	0.3-1.3	16	0.9 (0.23)	0.4-1.2
Day 26	17	1.0 (0.18)	0.7-1.3	17	0.9 (0.25)	0.4-1.3
Day 29	17	1.0 (0.27)	0.5-1.4	17	1.0 (0.30)	0.4-1.4
Last Visit	17	1.0 (0.27)	0.5-1.4	17	1.0 (0.30)	0.4-1.4

FIG. 55

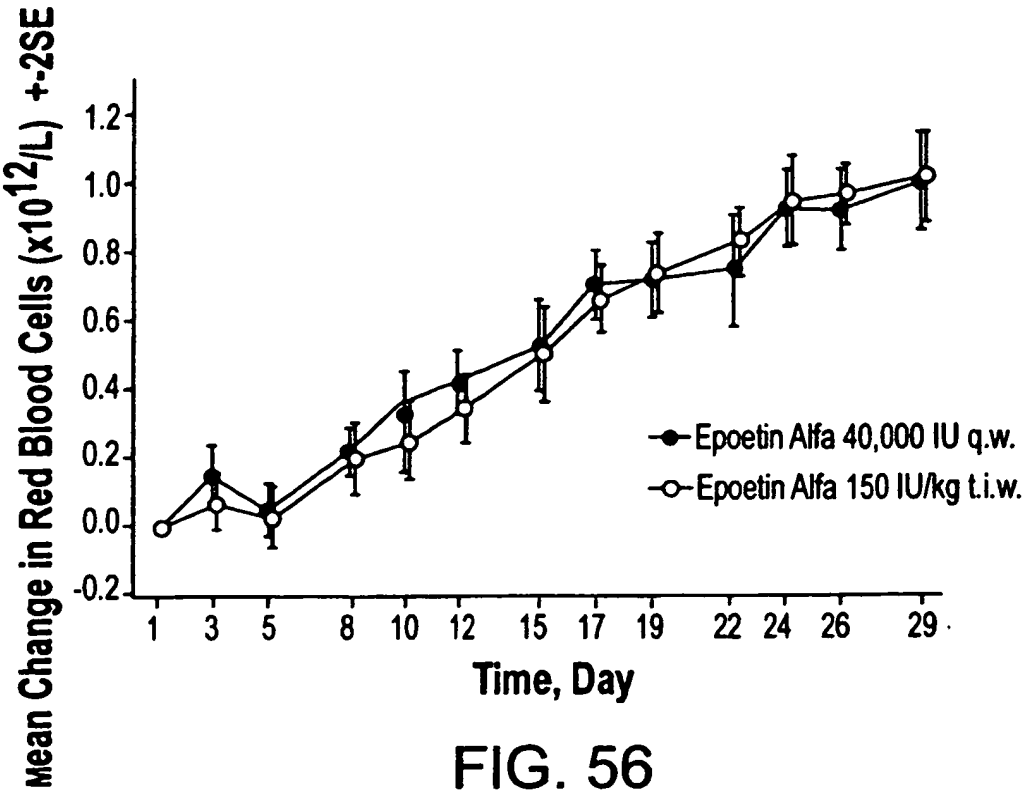

Mean Change in Red Blood Cells (x10^12/L) +-2SE
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
1
3
5
8
10
12
15
17
19
22
24
26
29
Time, Day
Epoetin Alfa 40,000 IU q.w.
Epoetin Alfa 150 IU/kg t.i.w.

FIG. 56

MEAN (SD) [%CV] PHARMACODYNAMIC PARAMETERS CORRECTED FOR BASELINE VALUE (EFFICACY POPULATION IN PROTOCOL EPO-PHI-373)

	AUC(RETI)[a] (%.d)		AUC(HEMO)[b] (g.d/dL)		AUC(RBC)[c] ($x10^{12}$.d/L)	
TREATMENT GROUP	MEAN (SD)	[%CV]	MEAN (SD)	[%CV]	MEAN (SD)	[%CV]
150 IU/kg t.i.w.						
Male (N=9)	55.1 (14.4)	[26.1%]	40.4 (13.0)	[32.2%]	13.4 (3.9)	[29.3%]
Female (N=8)	59.6 (21.3)	[35.7%]	51.1 (10.9)	[21.4%]	16.4 (4.4)	[26.7%]
All Subjects (N=17)	57.2 (17.5)	[30.6%]	45.4 (12.9)	[28.5%]	14.8 (4.3)	[29.0%]
40,000 IU q.w.						
Male (N=9)	58.8 (10.4)	[17.7%]	43.5 (1	1.6) [26.6%]	13.6 (4.3)	[31.3%]
Female (N=8)	68.4 (14.4)	[21.1%]	52.4 (15.0)	[28.6%]	16.9 (4.3)	[25.5%]
All Subjects (N=17)	63.3 (13.0)	[20.5%]	47.7 (13.6)	[28.6%]	15.1 (4.5)	[29.5%]
Ratio for All Subjects[d]	1.1	1	1.05		1.02	
All Females[e] (N=16)	64.0 (18.1)	[28.3%]	51.7 (12.7)	[g] [24.5%]	16.6 (4.2)	[g] [25.3%]
All Males[f] (N=18)	57.0 (12.3)	[21.6%]	41.9 (12.0)	[g] [28.7%]	13.5 (4.0)	[g] [29.5%]

%CV = percent coefficient of variation

[a] AUC of % reticulocytes over the one month study period and corrected for predose baseline value.

[b] AUC of hemoglobin over the one month study period and corrected for predose baseline value.

[c] AUC of red blood cells over the one month study period and corrected for predose baseline value.

[d] Ratios of 40,000 IU q.w. to 150 IU/kg t.i.w. mean parameter values for all subjects.

[e] Including all female subjects in both treatment groups.

[f] Including all male subjects in both treatment groups.

[g] Statistically different ($p<0.05$) between male and female subjects

FIG. 57

Body System Preferred Term	Epoetin Alfa 150 IU/kg t.i.w. (N=18)	Epoetin Alfa 40,000 IU q.w. (N=18)
Any adverse event	13 (72%)	12 (67%)
Body as a whole - general disorders	6 (33%)	7 (39%)
Pain	4 (22%)	5 (28%)
Fatigue	2 (11%)	1 (6%)
Enlarged abdomen	1 (6%)	0 (0%)
Allergic reaction	0 (0%)	1 (6%)
Back pain	0 (0%)	1 (6%)
Center & periph nerv syst disorders	6 (33%)	6 (33%)
Headache	5 (28%)	5 (28%)
Dizziness	1 (6%)	2 (11%)
Hyperesthesia	1 (6%)	0 (0%)
Hypertonia	1 (6%)	0 (0%)
Skin and appendage disorders	6 (33%)	3 (17%)
Erythematous rash	5 (28%)	2 (11%)
Rash	2 (11%)	1 (6%)
Skin disorder	0 (0%)	1 (6%)
Localized skin reaction	1 (6%)	0 (0%)
Gastro-intestinal system disorders	4 (22%)	2 (11%)
Abdominal pain	2 (11%)	0 (0%)
Nausea	2 (11%)	0 (0%)
Constipation	1 (6%)	0 (0%)
Diarrhea	1 (6%)	0 (0%)
Gastroenteritis	0 (0%)	1 (6%)
Gingivitis	0 (0%)	1 (6%)
Toothache	1 (6%)	0 (0%)
Application site disorders	5 (28%)	1 (6%)
Injection site bruising	3 (17%)	1 (6%)
Application site reaction	2 (11%)	0 (0%)
Injection site pain	1 (6%)	0 (0%)
Respiratory system disorders	2 (11%)	1 (6%)
Upper respiratory tract infection	2 (11%)	0 (0%)
Pharyngitis	0 (0%)	1 (6%)
Rhinitis	0 (0%)	1 (6%)
Metabolic nutritional disorders	1 (6%)	1 (6%)
Thirst	1 (6%)	0 (0%)
Xerophthalmia	0 (0%)	1 (6%)
Musculo-skeletal system disorders	2 (11%)	0 (0%)
Myalgia	1 (6%)	0 (0%)
Skeletal pain	1 (6%)	0 (0%)
Psychiatric disorders	0 (0%)	2 (11%)
Insomnia	0 (0%)	1 (6%)
Somnolence	0 (0%)	1 (6%)

FIG. 58

Body System Preferred Term	Epoetin Alfa 150 IU/kg t.i.w. (N=18)	Epoetin Afa 40,000 IU q.w. (N=18)
Heart rate and rhythm disorders	0 (0%)	1 (6%)
Palpitation	0 (0%)	1 (6%)
Female reproductive disorders	1 (11%)*	0 (0%)
Dysmenorrhea	1 (11%)*	0 (0%)
Other special senses disorders	1 (6%)	0 (0%)
Taste perversion	1 (6%)	0 (0%)
Vascular (extracardiac) disorders	1 (6%)	0 (0%)
Phlebitis	1 (6%)	0 (0%)
Vision disorders	1 (6%)	0 (0%)
Conjunctivitis	1 (6%)	0 (0%)

* Percentages taken as a percentage of the

2/2

FIG. 58

Mean (SD) Change from Baseline in Iron Profile (All Subjects in Protocol EPO-PHI-373)

	Epoetin Alfa 150 IU/kg t.i.w.			Epoetin Alfa 40,000 IU q.w.		
	N	Mean	(SD)	N	Mean	(SD)
Serum Iron (µg/dL)						
Baseline	18	97.1	(40.54)	18	102.7	(27.23)
Change from Baseline to Day 8	18	7.1	(79.56)	18	28.8	(95.05)
Change from Baseline to Day 15	18	34.7	(122.43)	17	49.6	(106.89)
Change from Baseline to Day 22	18	21.4	(108.34)	17	23.6	(95.73)
Change from Baseline to Day 29	17	-44.3	(43.76)	18	22.0	(78.18)
Change from Baseline to Last Visit	18	-33.5	(62.59)	18	22.0	(78.18)
Ferritin (ng/mL)						
Baseline	18	69.6	(25.17)	18	78.2	(31.36)
Change from Baseline to Day 8	18	-38.9	(13.13)	18	-37.9	(23.12)
Change from Baseline to Day 15	18	-37.6	(16.17)	17	-37.1	(31.52)
Change from Baseline to Day 22	18	-36.3	(22.79)	17	-43.0	(30.51)
Change from Baseline to Day 29	17	-41.5	(19.75)	18	-36.6	(37.18)
Change from Baseline to Last Visit	18	-38.1	(24.05)	18	-36.6	(37.18)
Transferrin Saturation (%)						
Baseline	18	35.6	(14.72)	18	37.3	(11.39)
Change from Baseline to Day 8	18	-0.2	(27.82)	18	5.4	(31.47)
Change from Baseline to Day 15	18	12.6	(41.69)	17	18.1	(34.06)
Change from Baseline to Day 22	18	6.2	(26.30)	17	8.6	(28.04)
Change from Baseline to Day 29	17	-17.0	(15.56)	18	-1.4	(19.86)
Change from Baseline to Last Visit	18	-15.7	(16.12)	18	-1.4	(19.86)

FIG. 59

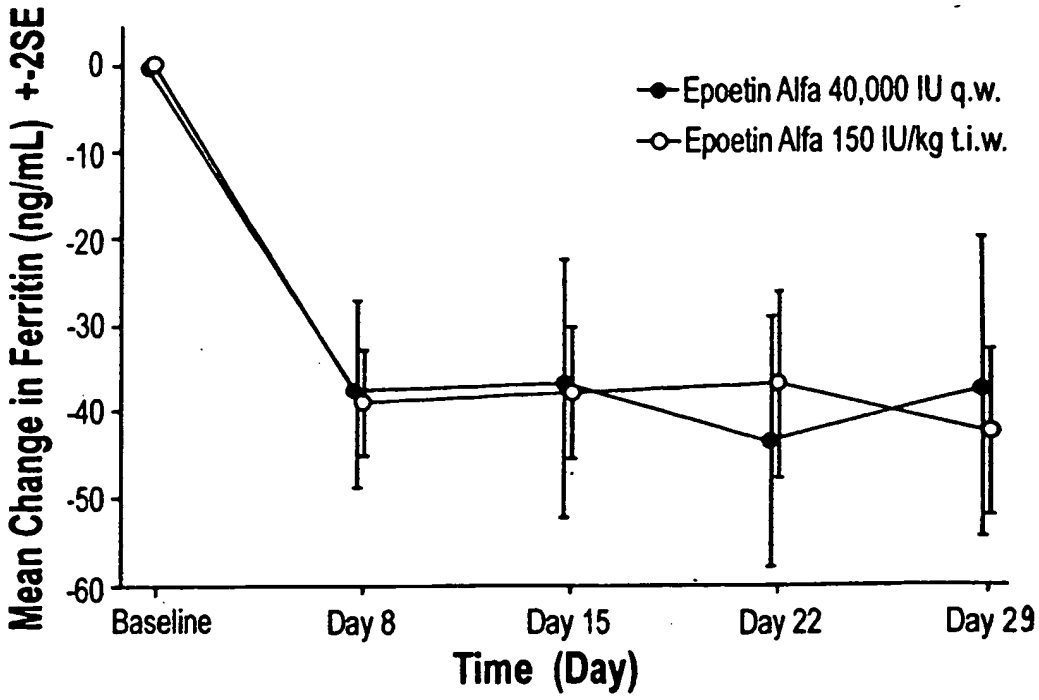

Mean Change in Ferritin (ng/mL) +-2SE
0
-10
-20
-30
-40
-50
-60
Baseline
Day 8
Day 15
Day 22
Day 29
Time (Day)
Epoetin Alfa 40,000 IU q.w.
Epoetin Alfa 150 IU/kg t.i.w.

FIG. 60

SUBJECTS WITH HIGH BLOOD PRESSURE VALUES [a]

SUBJECT	PRESTUDY	DAY 1	DAY 8	DAY 15	DAY 22	DAY 29
Epoetin Alfa 150 IU/kg t.i.w.						
1005	119/69	129/72	119/62	140/87[b]	127/70	121/72
2015	134/62	146/77[b]	144/64[b]	139/75	127/69	142/88[b]

[a] As indicated by a systolic blood pressure ≥ 140 mmHg or a diastolic pressure ≥95 mmHg.

[b] Indicates a systolic blood pressure ≥ 140 mmHg.

FIG. 61

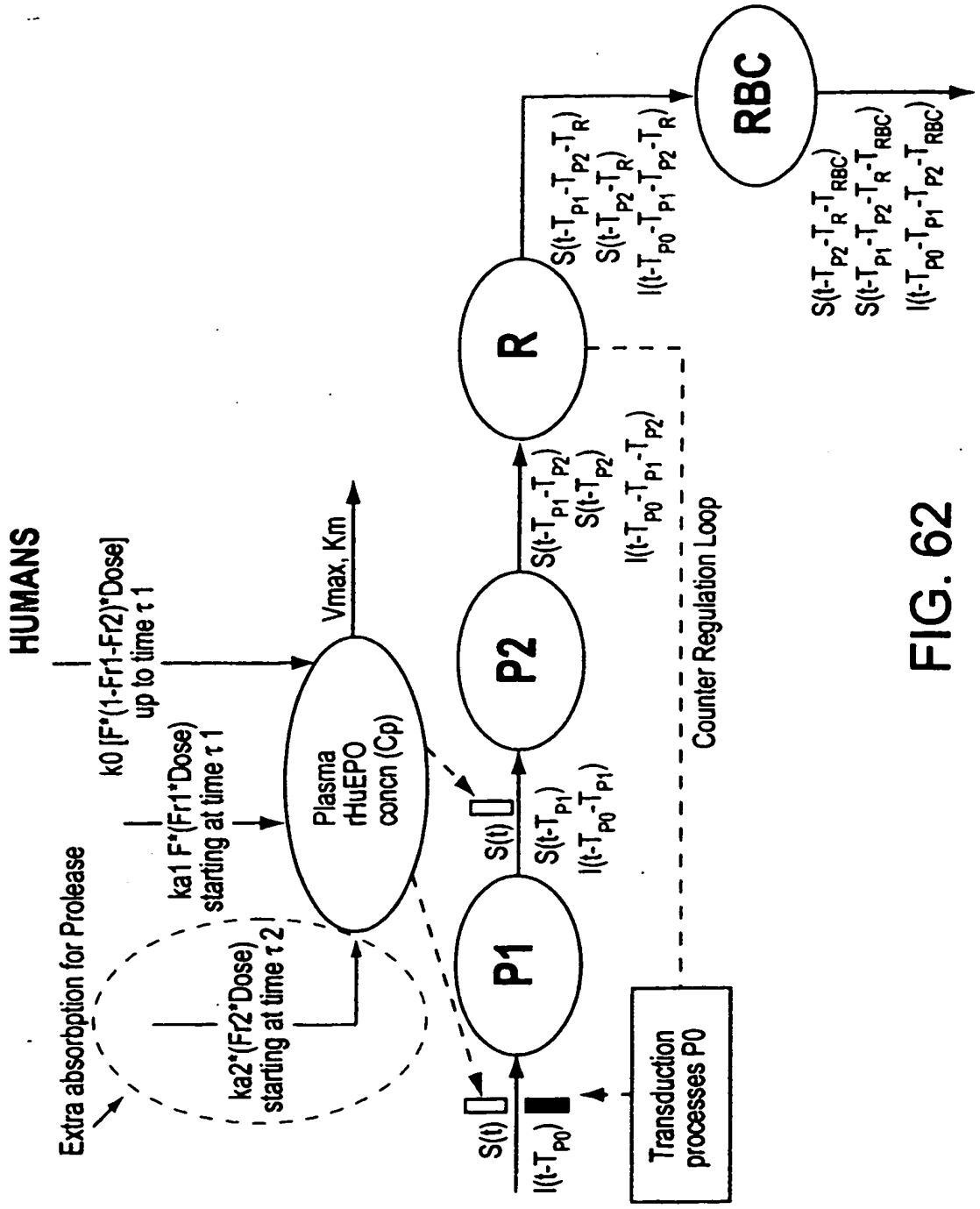

HUMANS
Extra absorption for Prolease
k0 [F*(1-Fr1-Fr2)*Dose] up to time τ 1
ka1 F*(Fr1*Dose) starting at time τ 1
ka2*(Fr2*Dose) starting at time τ 2
Plasma rHuEPO concn (Cp)
Vmax, Km
P1
P2
R
RBC
S(t)
I(t-T_P0)
S(t-T_P1)
I(t-T_P0-T_P1)
S(t-T_P1-T_P2)
S(t-T_P2)
I(t-T_P0-T_P1-T_P2)
S(t-T_P1-T_P2-T_R)
S(t-T_P2-T_R)
I(t-T_P0-T_P1-T_P2-T_R)
S(t-T_P2-T_R-T_RBC)
S(t-T_P1-T_P2-T_R-T_RBC)
I(t-T_P0-T_P1-T_P2-T_RBC)
Transduction processes P0
Counter Regulation Loop

FIG. 62

PHARMACOKINETIC PARAMETERS AFTER rHuEpo DOSING

	EPREX *single dose*	PROLEASE
ka1 (hr^{-1})	0.0219	0.0084
ka2 (hr^{-1})	-	0.0027
fr1	0.1308	0.3643
fr2	-	0.0782
kel (hr^{-1})	-	0.0027
Vmax (IU/kg/hr)	138.5	-
Km (IU/L)	20940	-
Vd (L/kg)	0.0558	0.2072
Tau1 (hr)	44	45.18
Tau2 (hr)	-	215.2
F=0.3884+0.00024952*DOSE		

For EPREX *150 IU/kg/t.i.w*	*600 IU/kg/wk*
0.1193	-
10	32.15
F=0.25	

FIG. 63

PHARMACODYNAMIC PARAMETERS AFTER rHuEpo DOSING

PHYSIOLOGICAL/LIFESPAN PARAMETERS ESTIMATED FROM SINGLE DOSE DATA

TP1	88.17
TP2	10.76
*RL	116.6
**IC50	38.71
TPO	137.5

EPREX

single dose	multiple dosing	
* (males)	males	females
** 4.251	8.186	4.178
26.53	61.15	57.3

FIG. 64

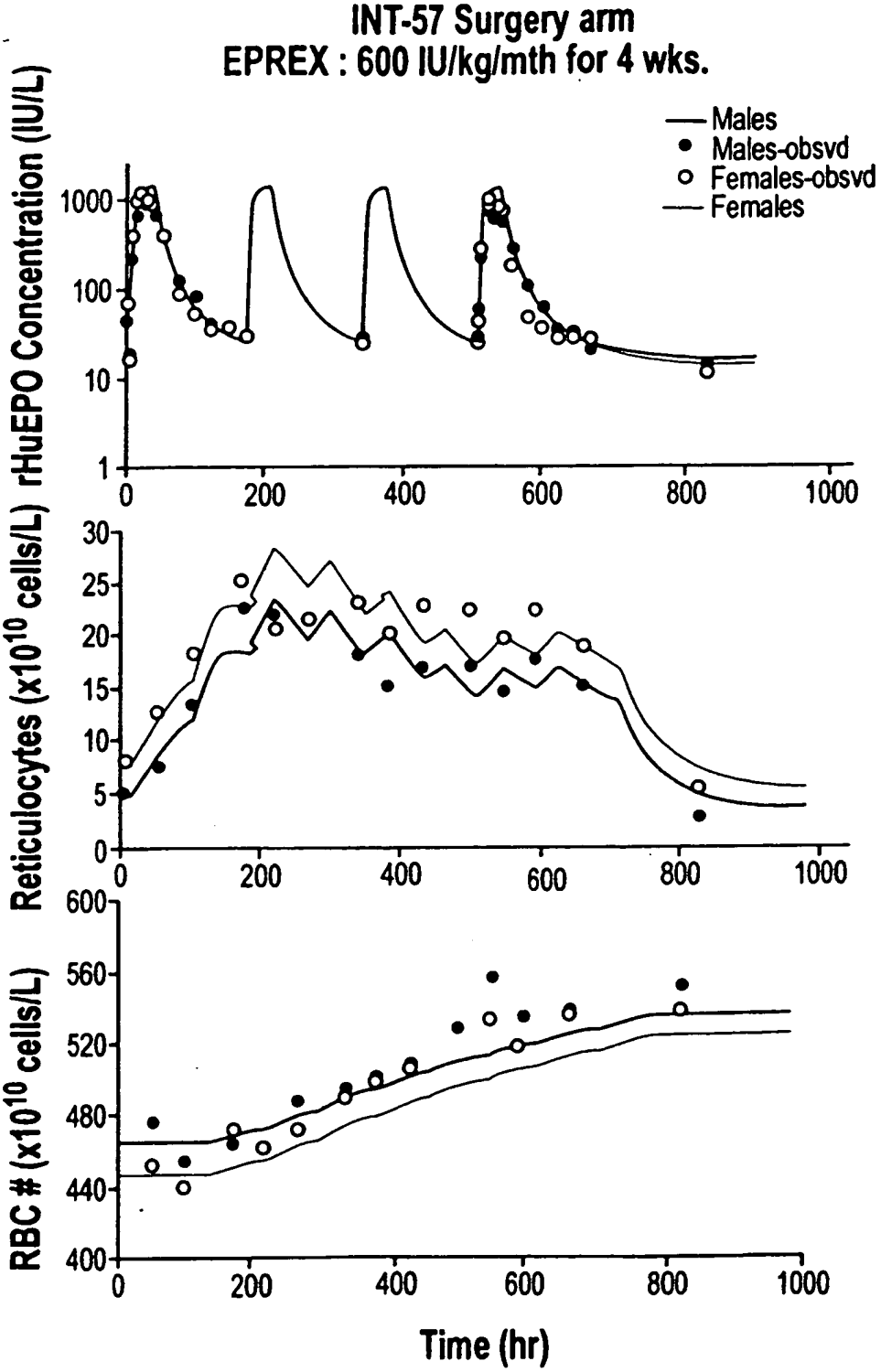

INT-57 Surgery arm
EPREX : 600 IU/kg/mth for 4 wks.
Males
Males-obsvd
Females-obsvd
Females
rHuEPO Concentration (IU/L)
1000
100
10
1
0
200
400
600
800
1000
Reticulocytes (x10^10 cells/L)
30
25
20
15
10
5
0
RBC # (x10^10 cells/L)
600
560
520
480
440
400
Time (hr)

FIG. 65

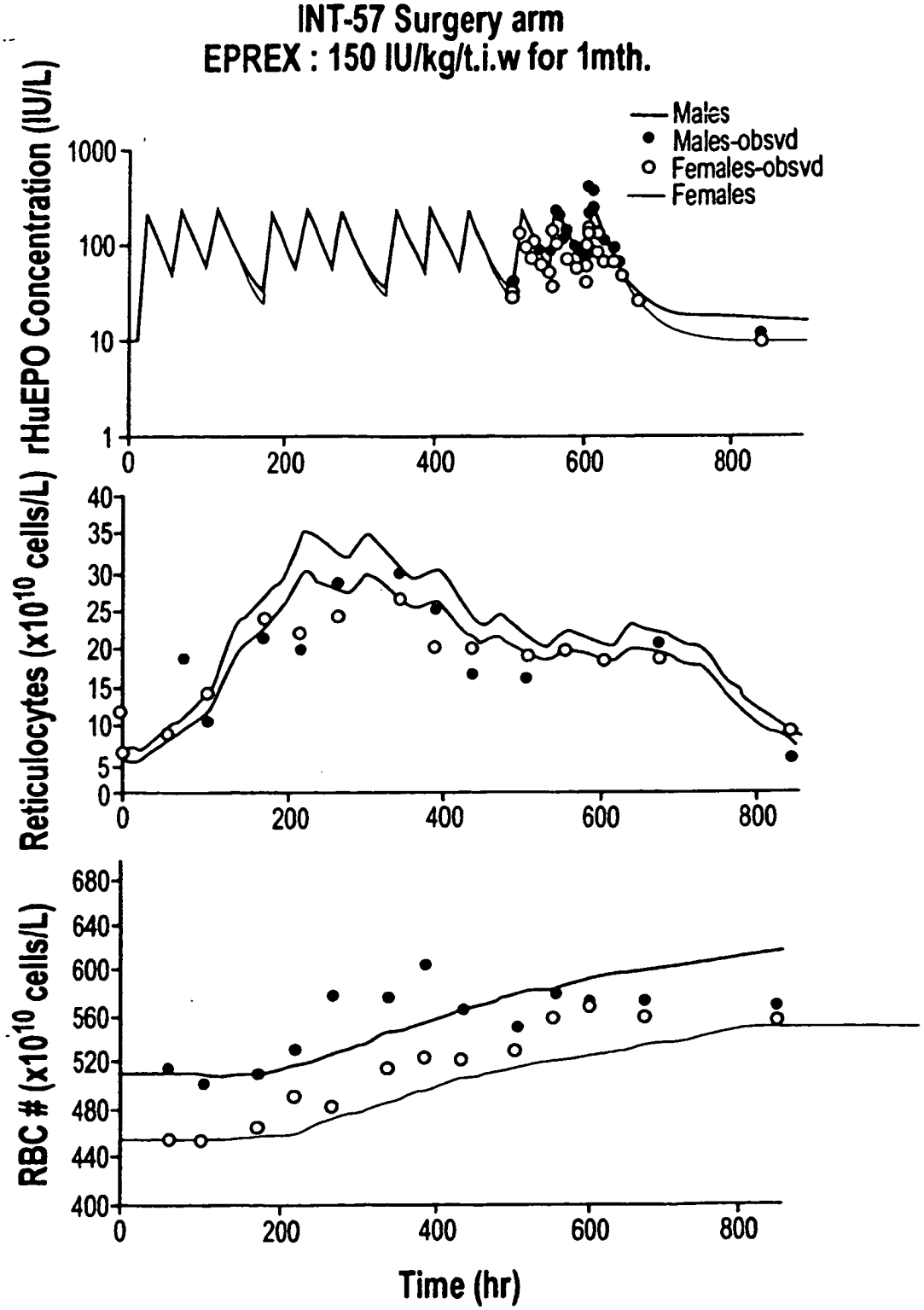

INT-57 Surgery arm
EPREX : 150 IU/kg/t.i.w for 1mth.
Males
Males-obsvd
Females-obsvd
Females
rHuEPO Concentration (IU/L)
1000
100
10
1
0
200
400
600
800
Reticulocytes (x10^10 cells/L)
40
35
30
25
20
15
10
5
0
RBC # (x10^10 cells/L)
680
640
600
560
520
480
440
400
Time (hr)

FIG. 66

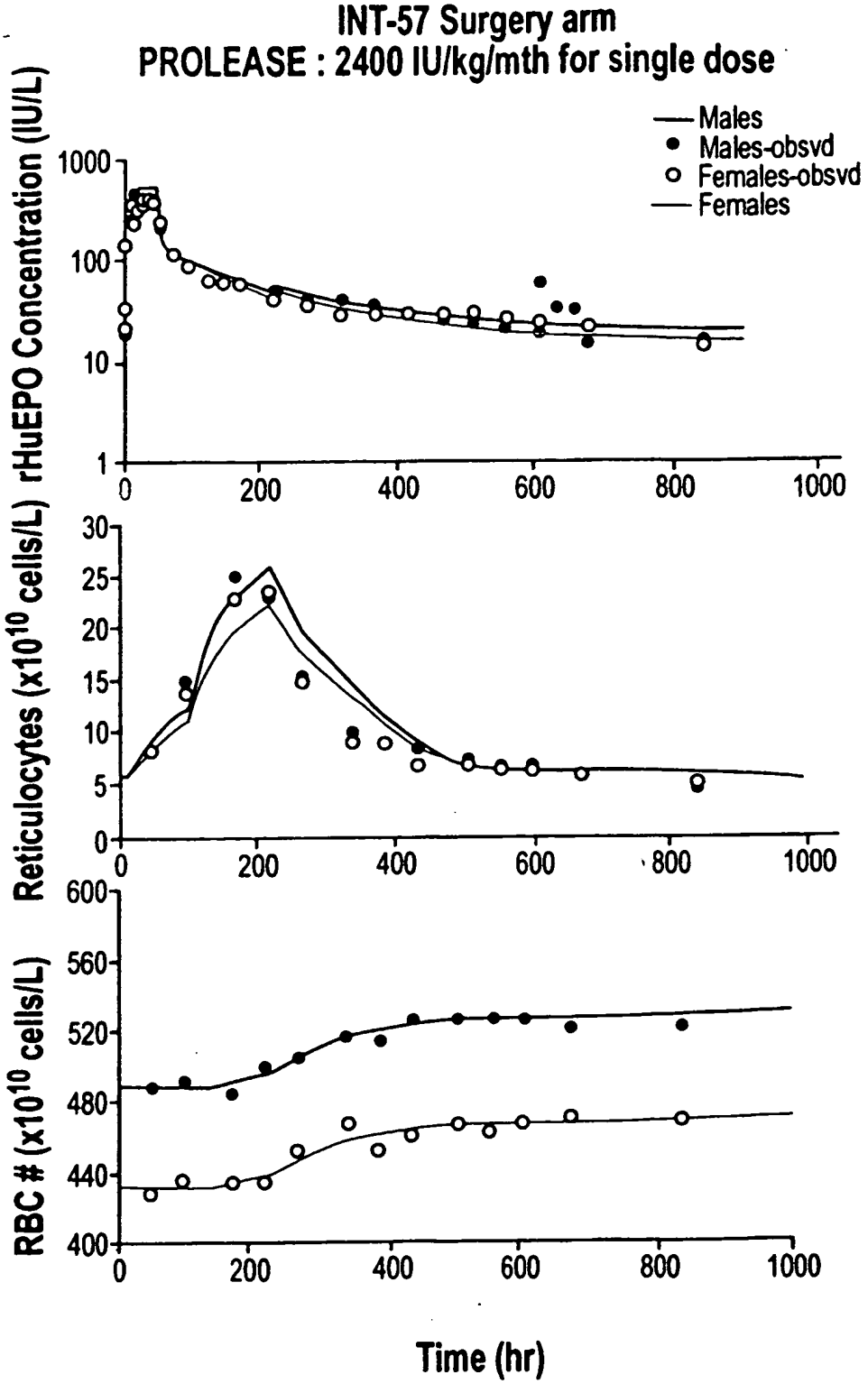

INT-57 Surgery arm
PROLEASE : 2400 IU/kg/mth for single dose
Males
Males-obsvd
Females-obsvd
Females
rHuEPO Concentration (IU/L)
1000
100
10
1
0
200
400
600
800
1000
Reticulocytes (x10^10 cells/L)
30
25
20
15
10
5
0
RBC # (x10^10 cells/L)
600
560
520
480
440
400
Time (hr)

FIG. 67

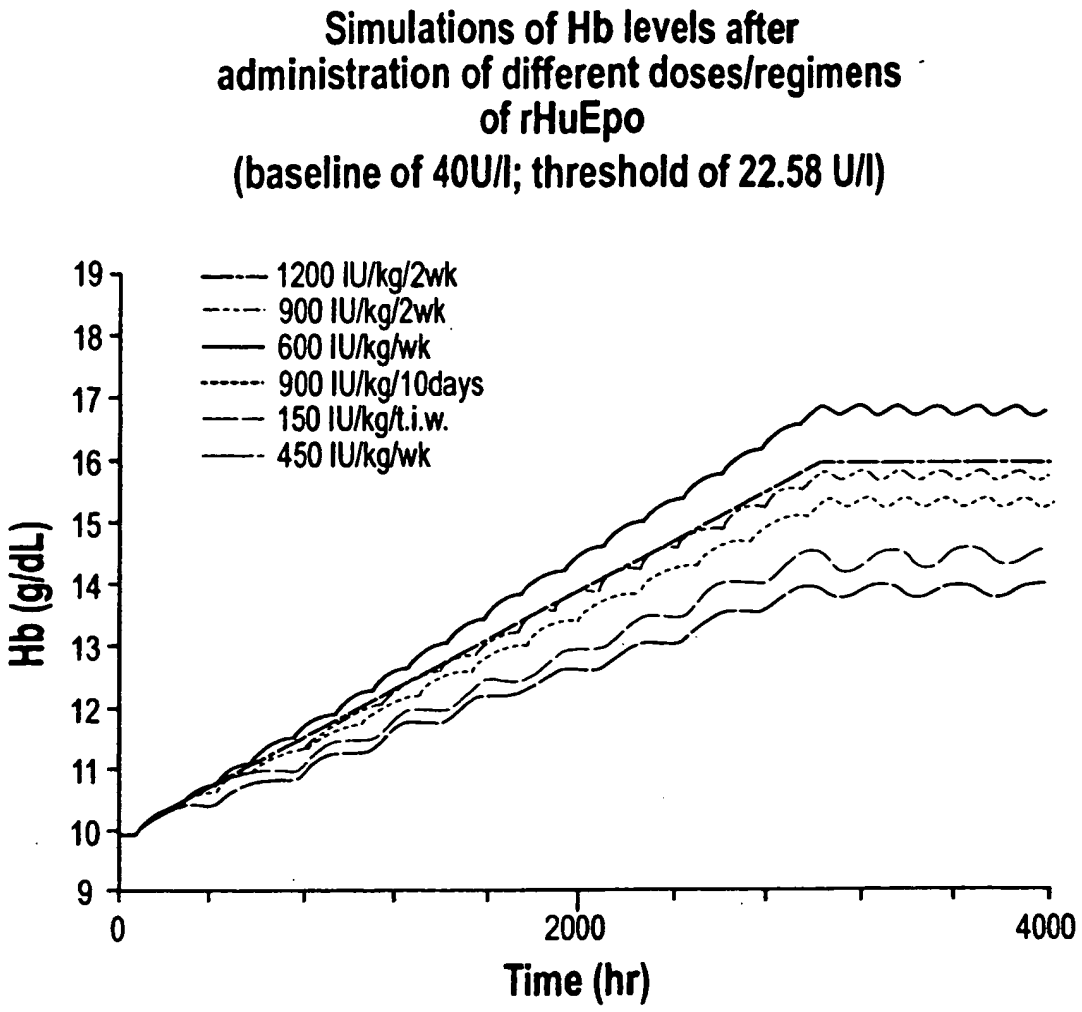

Simulations of Hb levels after administration of different doses/regimens of rHuEpo
(baseline of 40U/l; threshold of 22.58 U/l)
1200 IU/kg/2wk
900 IU/kg/2wk
600 IU/kg/wk
900 IU/kg/10days
150 IU/kg/t.i.w.
450 IU/kg/wk
Hb (g/dL)
19
18
17
16
15
14
13
12
11
10
9
0
2000
4000
Time (hr)

FIG.68

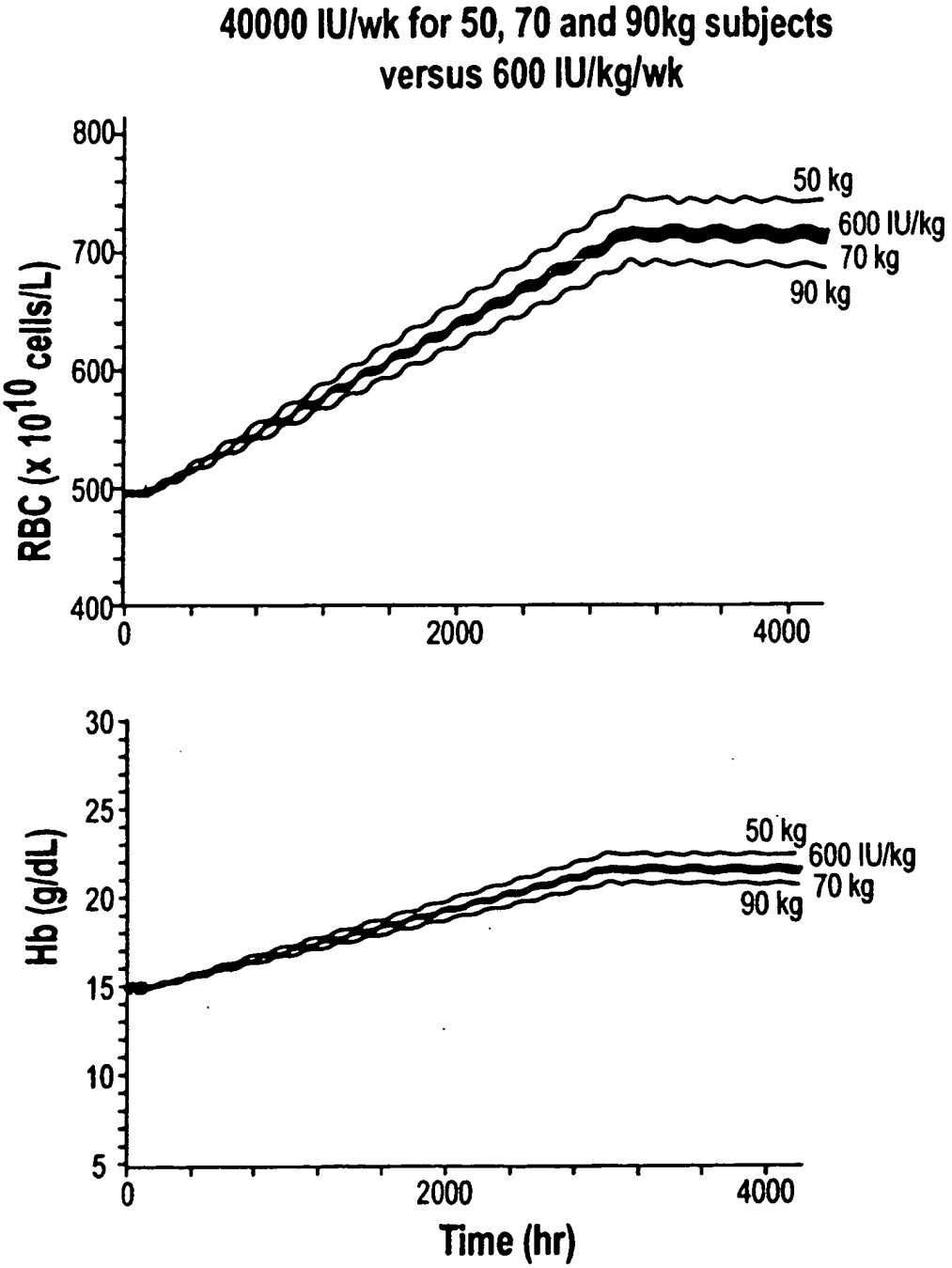

40000 IU/wk for 50, 70 and 90kg subjects versus 600 IU/kg/wk
RBC (x 10^10 cells/L)
800
700
600
500
400
0
2000
4000
50 kg
600 IU/kg
70 kg
90 kg
Hb (g/dL)
30
25
20
15
10
5
0
2000
4000
50 kg
600 IU/kg
70 kg
90 kg
Time (hr)

FIG.69

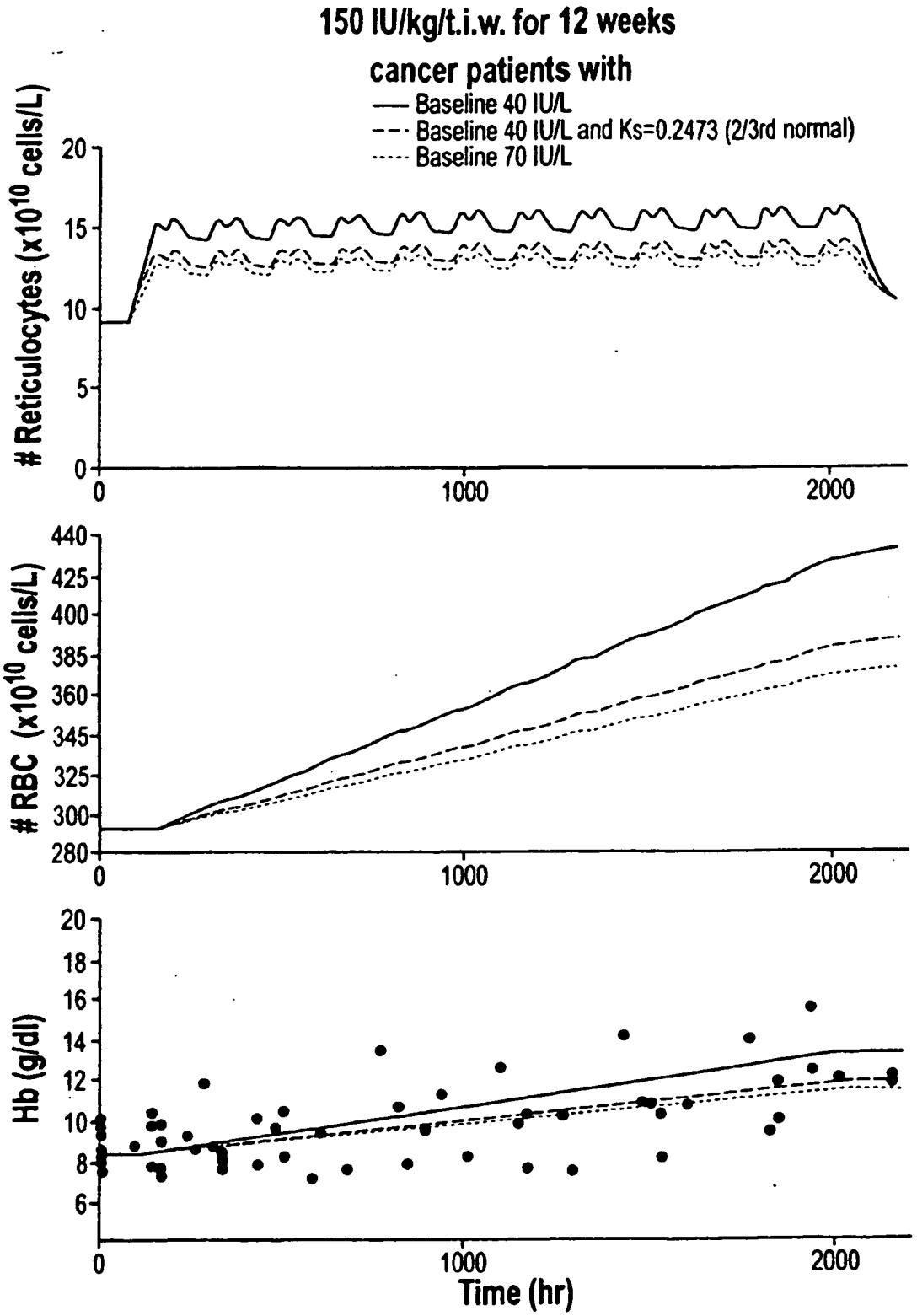

150 IU/kg/t.i.w. for 12 weeks
cancer patients with
Baseline 40 IU/L
Baseline 40 IU/L and Ks=0.2473 (2/3rd normal)
Baseline 70 IU/L
Reticulocytes (x10^10 cells/L)
20
15
10
5
0
0
1000
2000
RBC (x10^10 cells/L)
440
425
400
385
360
345
325
300
280
0
1000
2000
Hb (g/dl)
20
18
16
14
12
10
8
6
0
1000
2000
Time (hr)

FIG. 70A

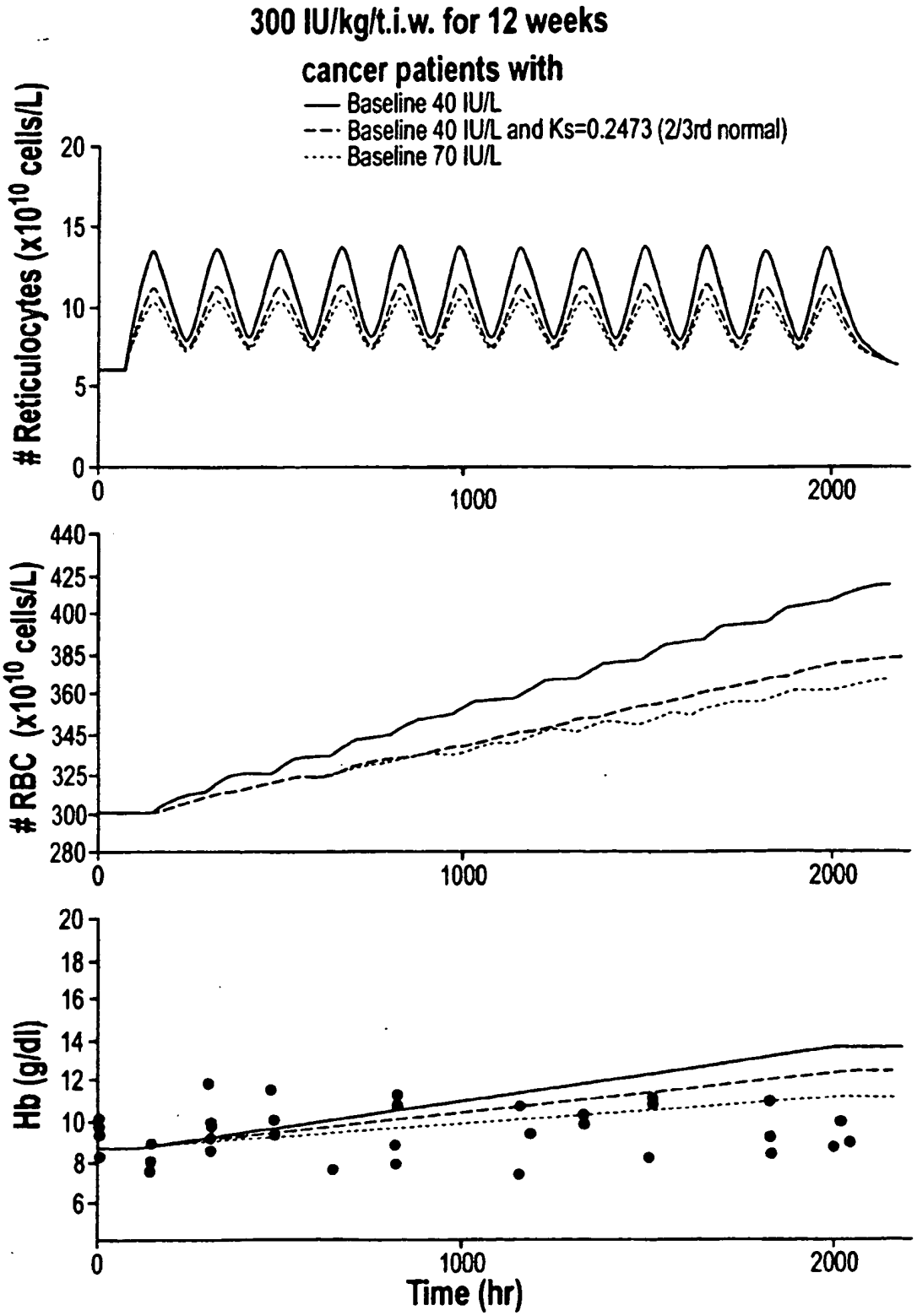

300 IU/kg/t.i.w. for 12 weeks
cancer patients with
Baseline 40 IU/L
Baseline 40 IU/L and Ks=0.2473 (2/3rd normal)
Baseline 70 IU/L
Reticulocytes (x10^10 cells/L)
20
15
10
5
0
0
1000
2000
RBC (x10^10 cells/L)
440
425
400
385
360
345
325
300
280
0
1000
2000
Hb (g/dl)
20
18
16
14
12
10
8
6
0
1000
2000
Time (hr)

FIG. 70B

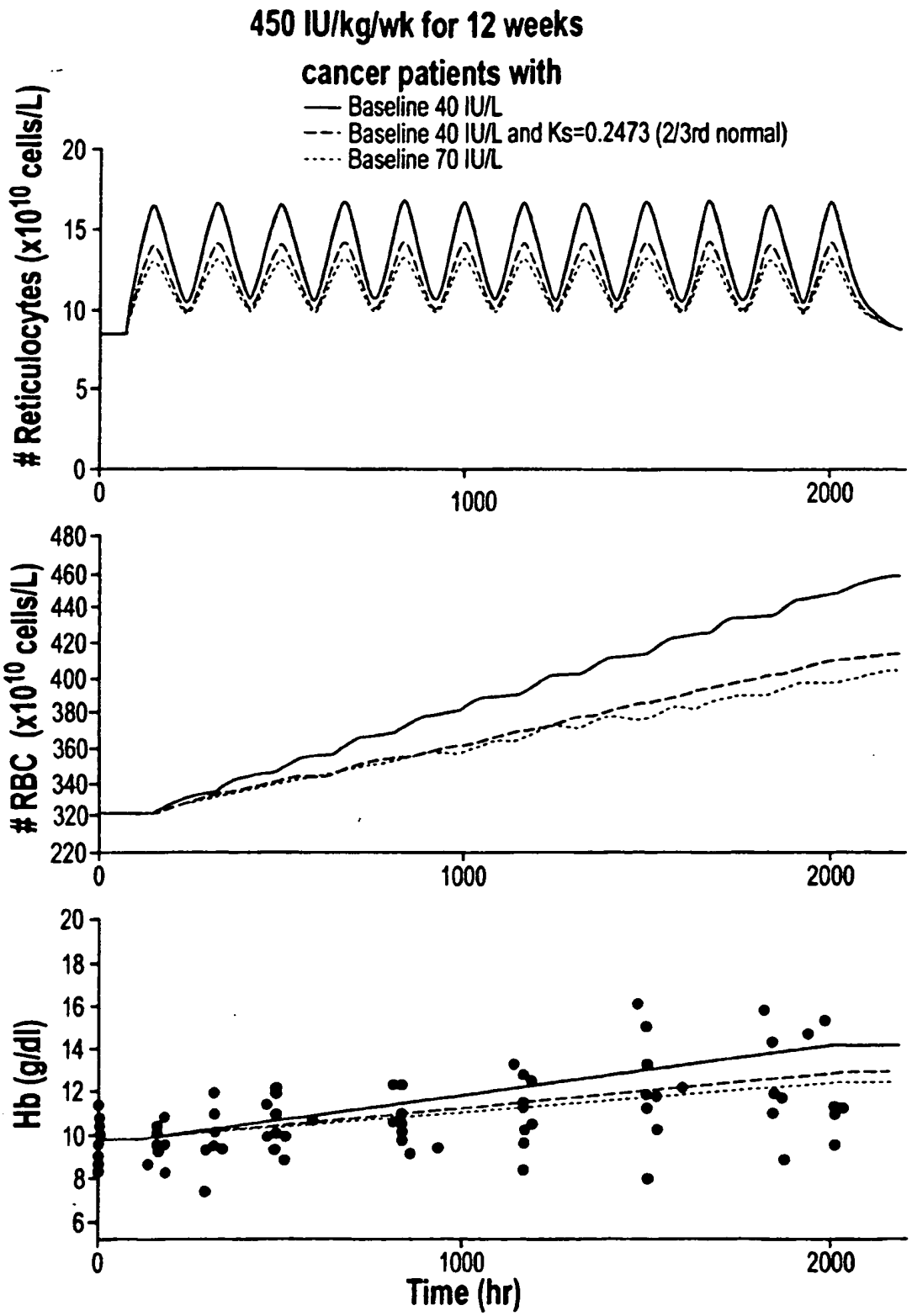

450 IU/kg/wk for 12 weeks
cancer patients with
Baseline 40 IU/L
Baseline 40 IU/L and Ks=0.2473 (2/3rd normal)
Baseline 70 IU/L
Reticulocytes (x10^10 cells/L)
20
15
10
5
0
0
1000
2000
RBC (x10^10 cells/L)
480
460
440
420
400
380
360
340
320
220
0
1000
2000
Hb (g/dl)
20
18
16
14
12
10
8
6
0
1000
2000
Time (hr)

FIG. 70C

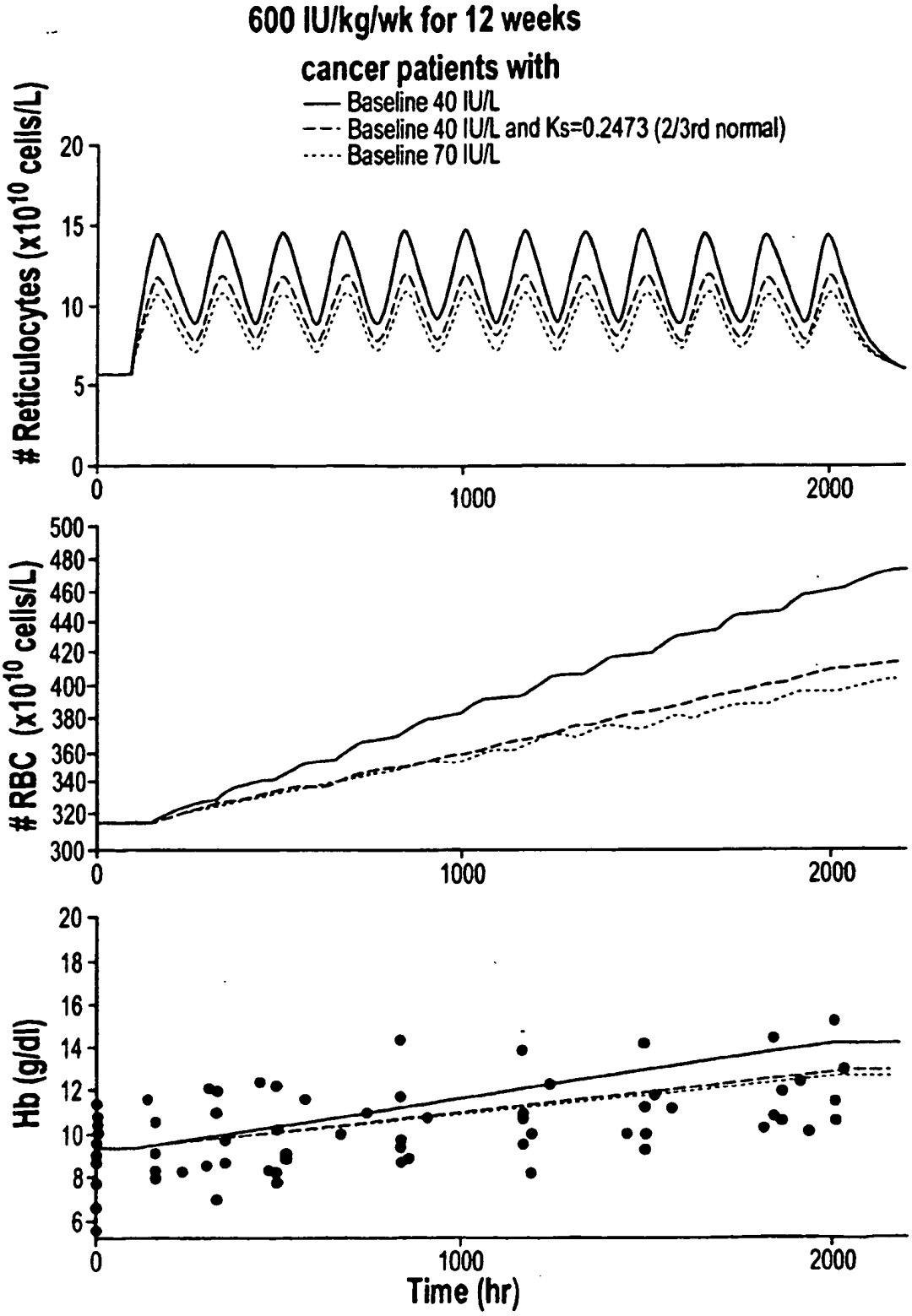

600 IU/kg/wk for 12 weeks
cancer patients with
Baseline 40 IU/L
Baseline 40 IU/L and Ks=0.2473 (2/3rd normal)
Baseline 70 IU/L
Reticulocytes (x10^10 cells/L)
20
15
10
5
0
0
1000
2000
RBC (x10^10 cells/L)
500
480
460
440
420
400
380
360
340
320
300
0
1000
2000
Hb (g/dl)
20
18
16
14
12
10
8
6
0
1000
2000
Time (hr)

FIG. 70D

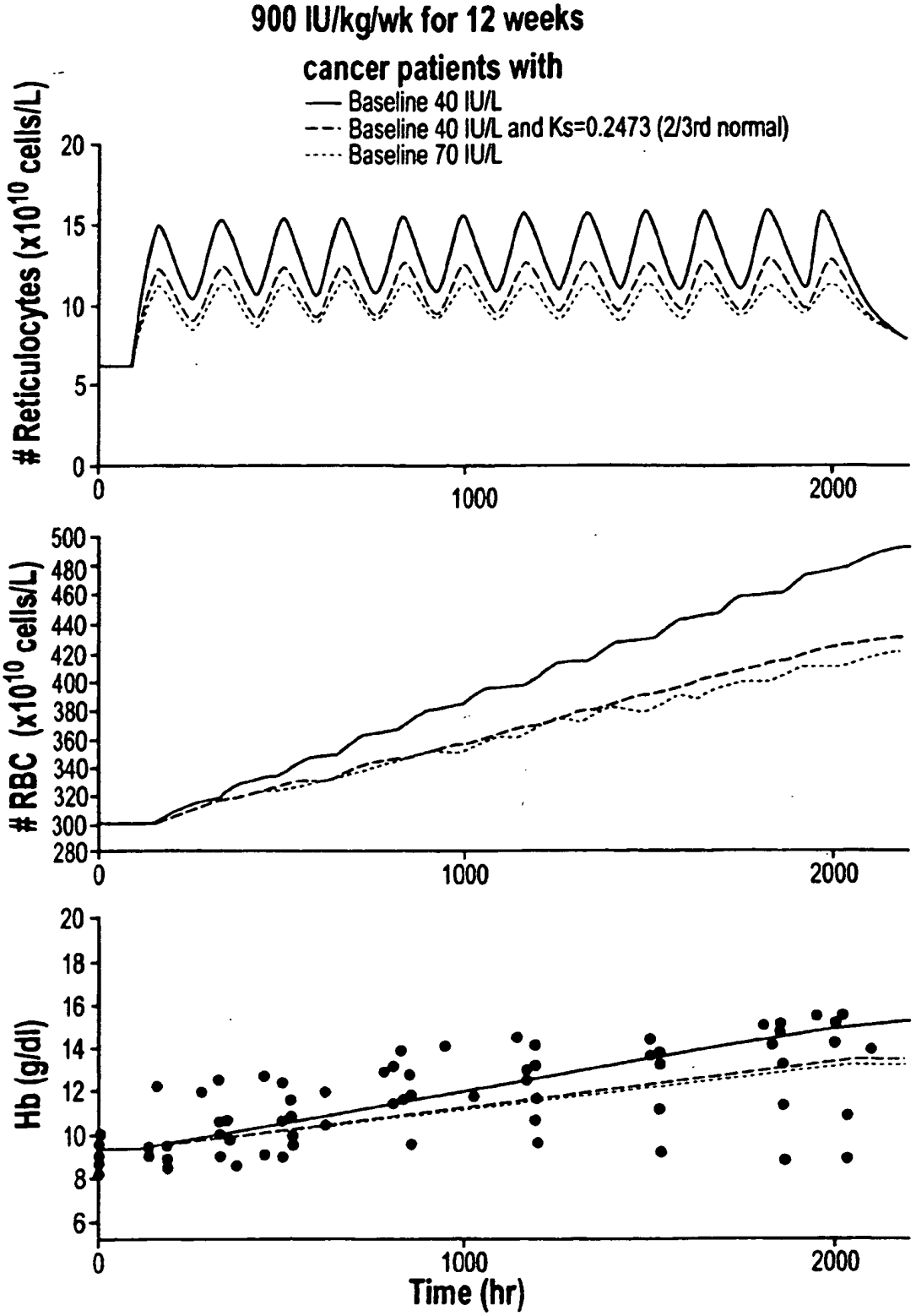

900 IU/kg/wk for 12 weeks
cancer patients with
Baseline 40 IU/L
Baseline 40 IU/L and Ks=0.2473 (2/3rd normal)
Baseline 70 IU/L
Reticulocytes (x10^10 cells/L)
20
15
10
5
0
0
1000
2000
RBC (x10^10 cells/L)
500
480
460
440
420
400
380
360
340
320
300
280
0
1000
2000
Hb (g/dl)
20
18
16
14
12
10
8
6
0
1000
2000
Time (hr)

FIG. 70E

DM00004
Mean Hemoglobin Time-Concentration Profiles

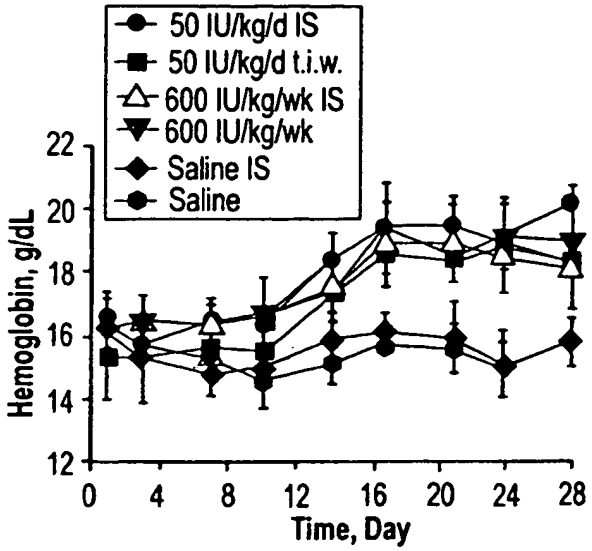


FIG. 71

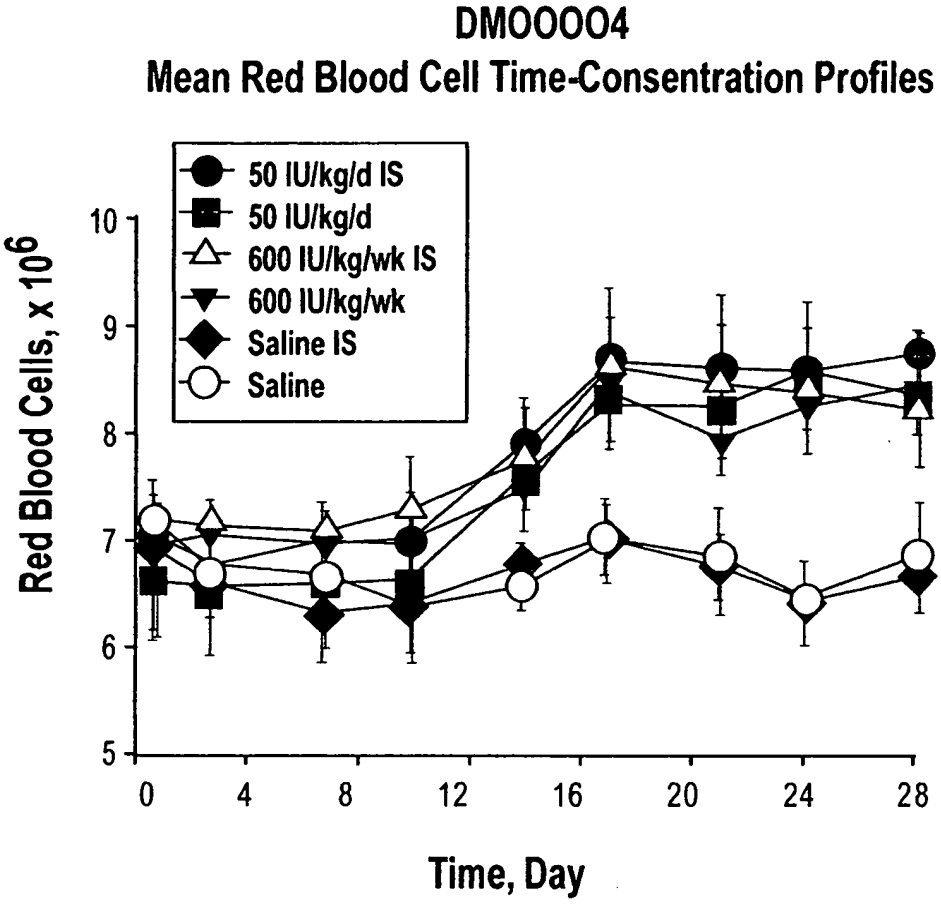

DM00004
Mean Red Blood Cell Time-Consentration Profiles
50 IU/kg/d IS
50 IU/kg/d
600 IU/kg/wk IS
600 IU/kg/wk
Saline IS
Saline
Red Blood Cells, x 10^6
10
9
8
7
6
5
0
4
8
12
16
20
24
28
Time, Day

FIG.72

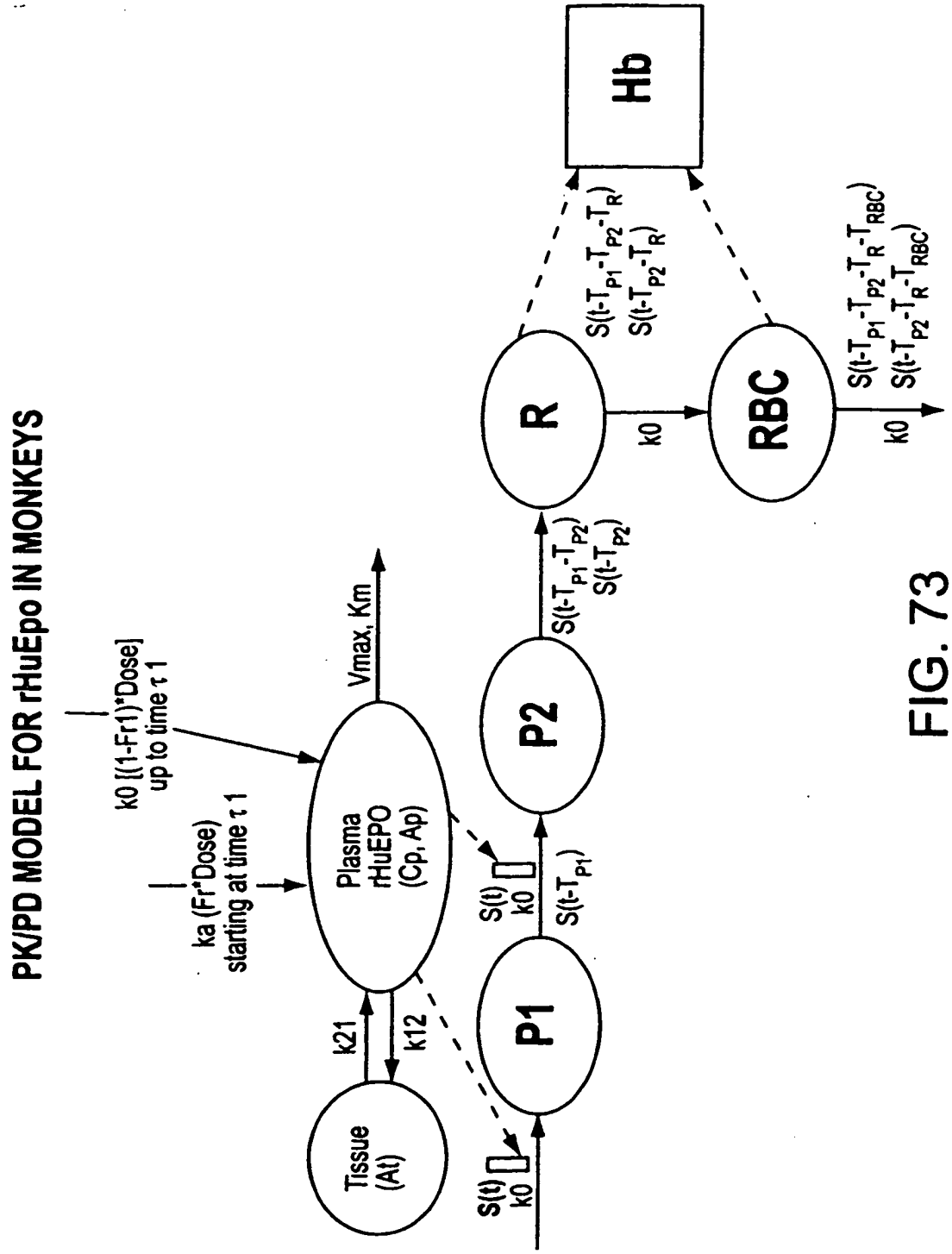

PK/PD MODEL FOR rHuEpo IN MONKEYS
k0 [(1-Fr1)*Dose] up to time τ 1
ka (Fr*Dose) starting at time τ 1
Plasma rHuEPO (Cp, Ap)
Vmax, Km
Tissue (At)
k21
k12
S(t) k0
S(t-TP1)
P1
P2
S(t-TP1-TP2) S(t-TP2)
R
S(t-TP1-TP2-TR) S(t-TP2-TR)
k0
RBC
S(t-TP1-TP2-TR-TRBC) S(t-TP2-TR-TRBC)
k0
Hb

FIG. 73

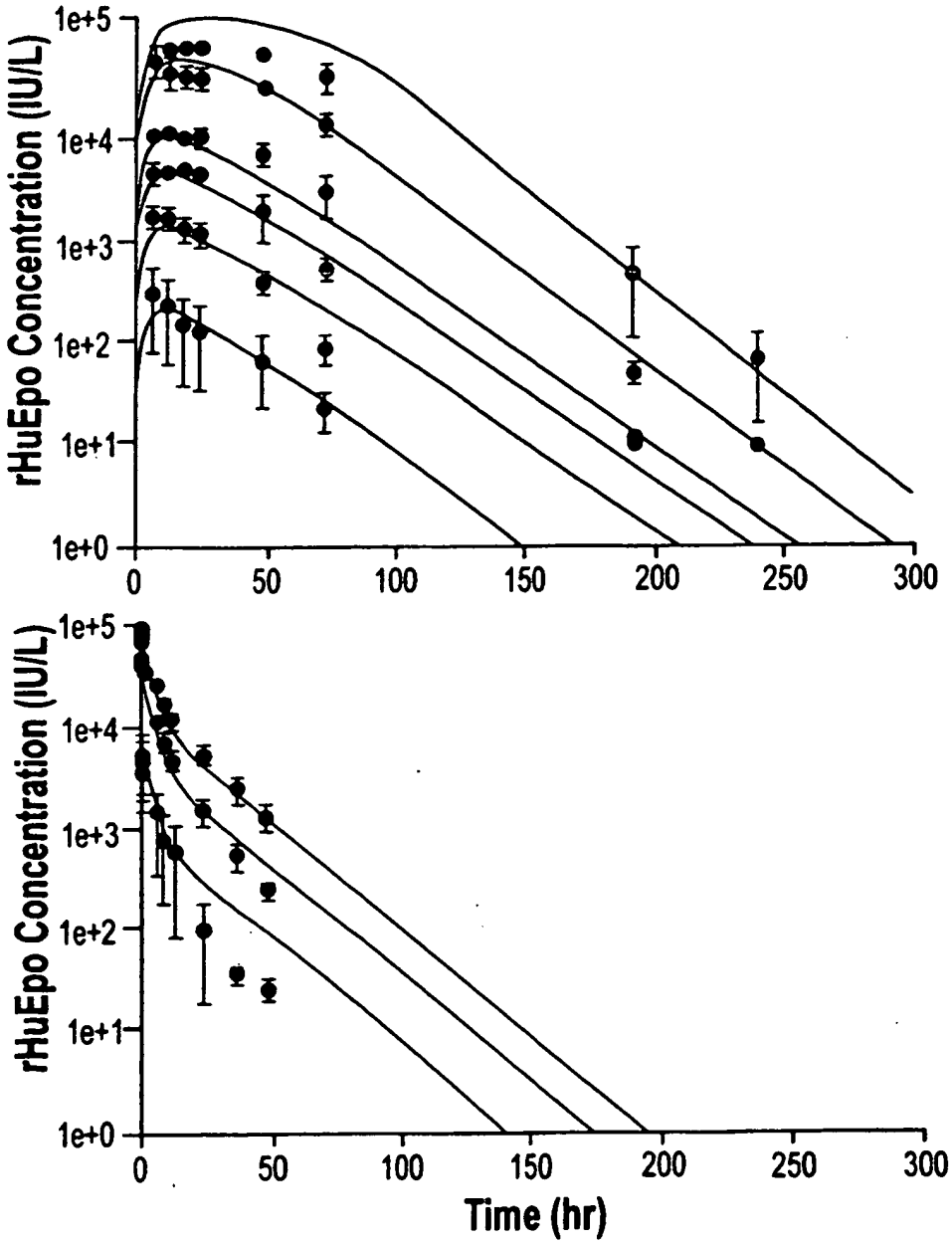

rHuEpo Concentration (IU/L)
1e+5
1e+4
1e+3
1e+2
1e+1
1e+0
0
50
100
150
200
250
300
rHuEpo Concentration (IU/L)
1e+5
1e+4
1e+3
1e+2
1e+1
1e+0
0
50
100
150
200
250
300
Time (hr)

FIG. 74

PHARMACOKINETIC PARAMETERS IN MONKEYS

	EPREX
Vmax (IU/kg/hr)	480.3
Km (IU/L)	35190
Vd (L/kg)	0.05689
k12 (hr-1)	0.1192
k21 (hr-1)	0.07916
Tau (hr)	10
ka (hr-1)	0.04427
ka (hr-1)-lowest dose	0.05255
Fr	0.6452
F (400 IU/kg dose)	0.2666
F (1000 IU/kg dose)	0.7348
F (higher doses)	1

FIG. 75

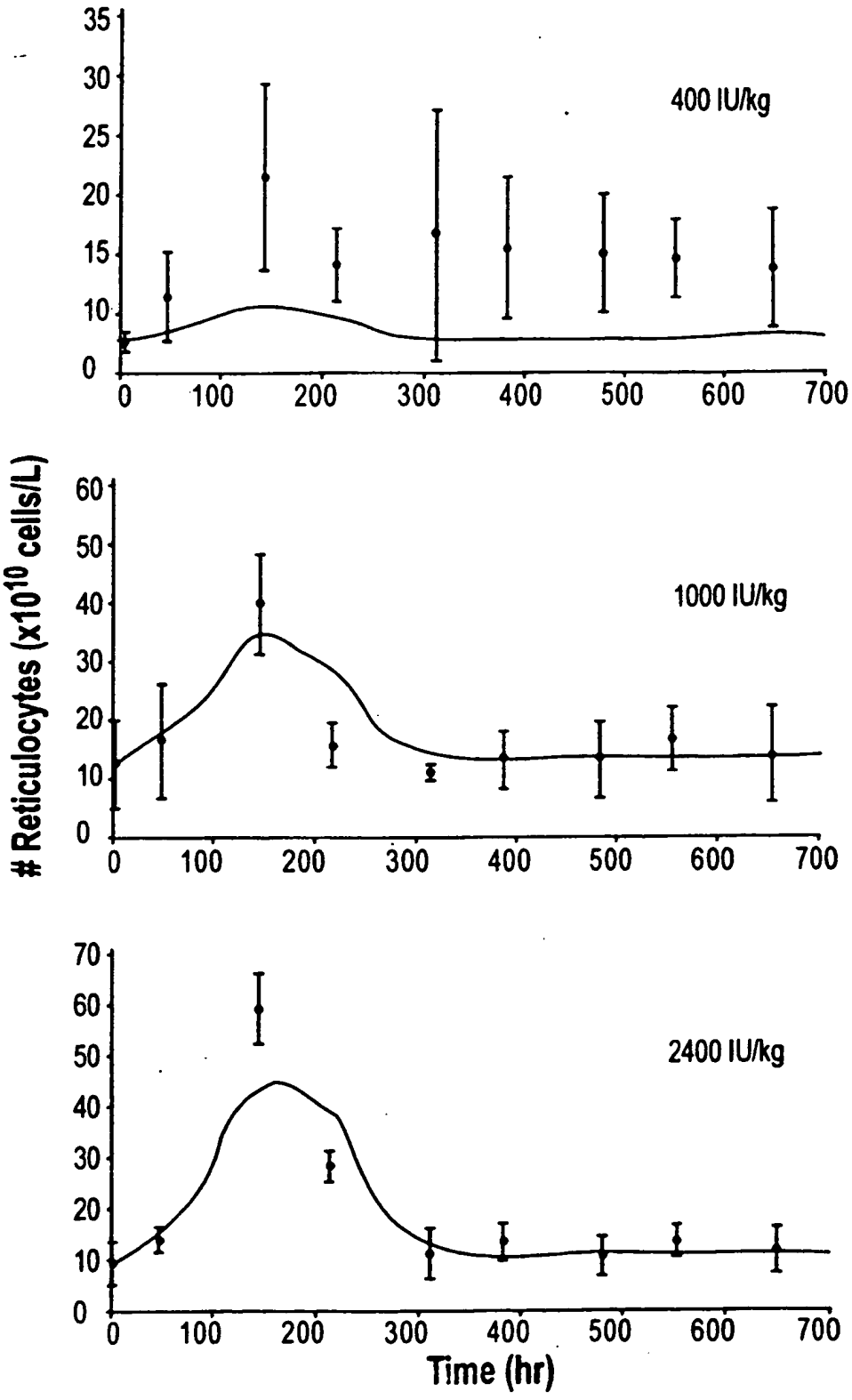

400 IU/kg
1000 IU/kg
2400 IU/kg
Reticulocytes (x10^10 cells/L)
Time (hr)
0
100
200
300
400
500
600
700

FIG. 76A

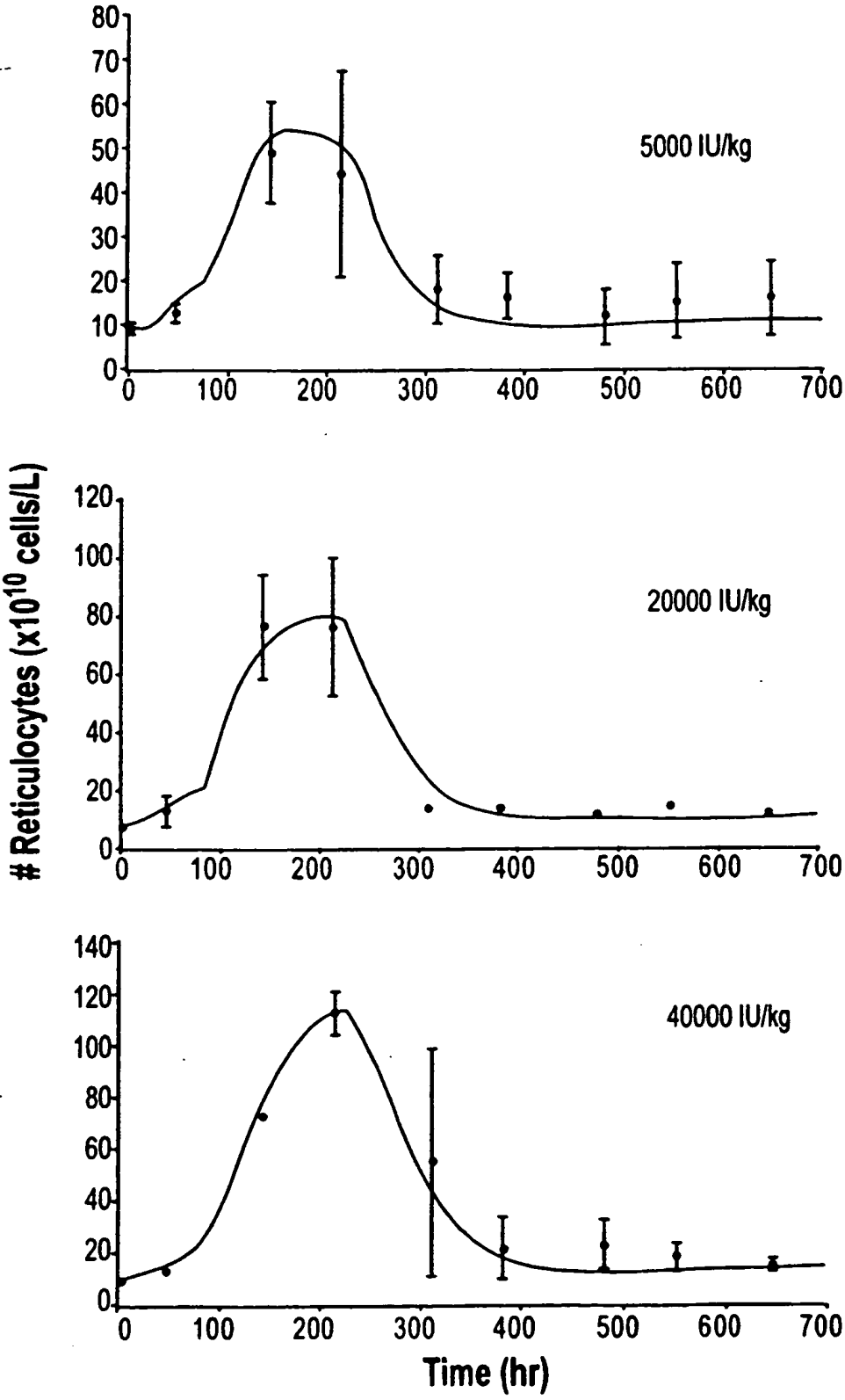

5000 IU/kg
20000 IU/kg
40000 IU/kg
Reticulocytes (x10^10 cells/L)
Time (hr)
0
10
20
30
40
50
60
70
80
100
120
140
100
200
300
400
500
600
700

FIG. 76B

PHARMACODYNAMIC PARAMETERS IN MONKEYS

	EPREX
TP1 (h)	70.38
TP2 (h)	14.95
RL (h)	141.6
Smax	3.133
SC50 (IU/L)	842.5

FIG. 77

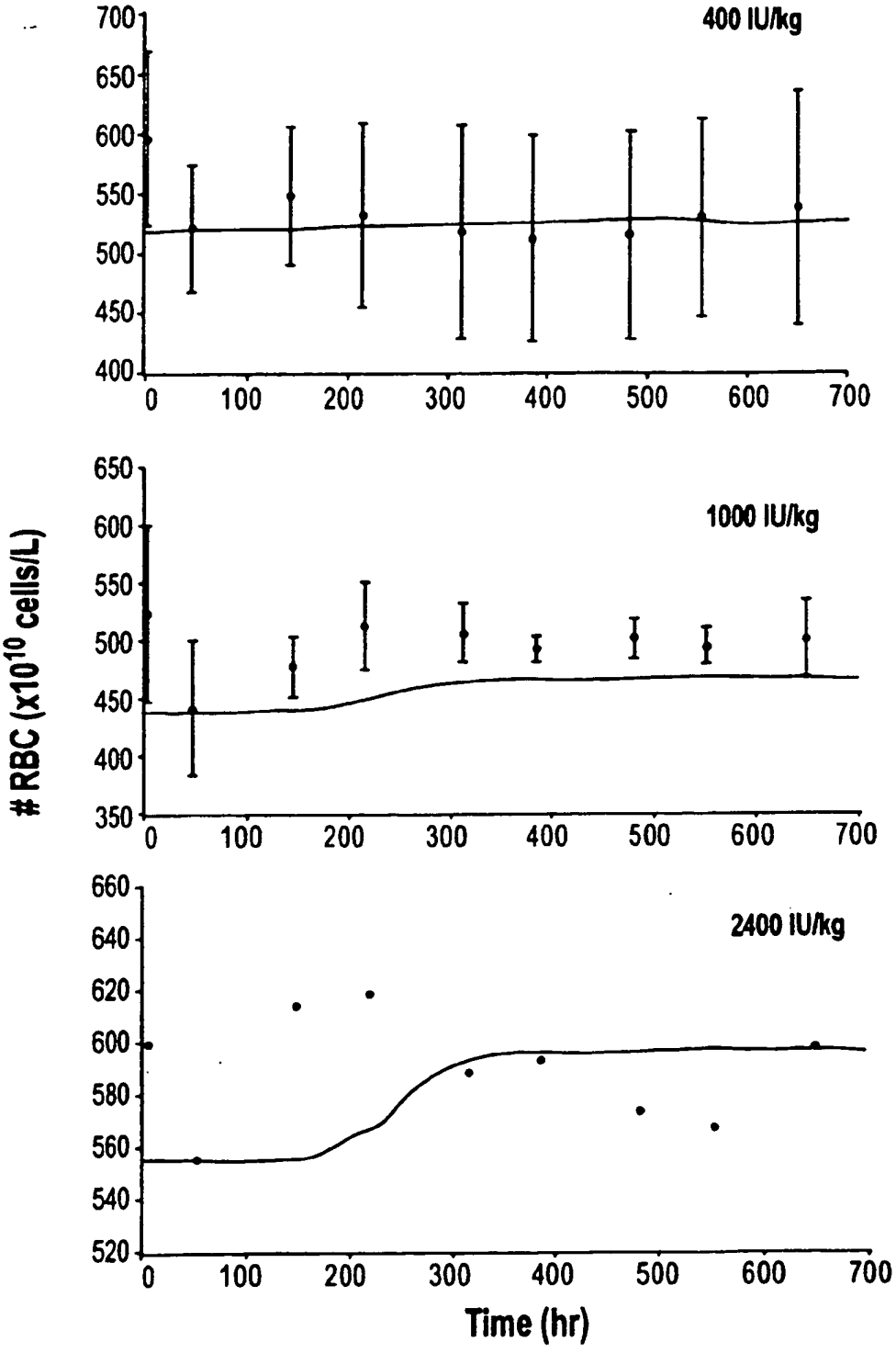


FIG. 78A

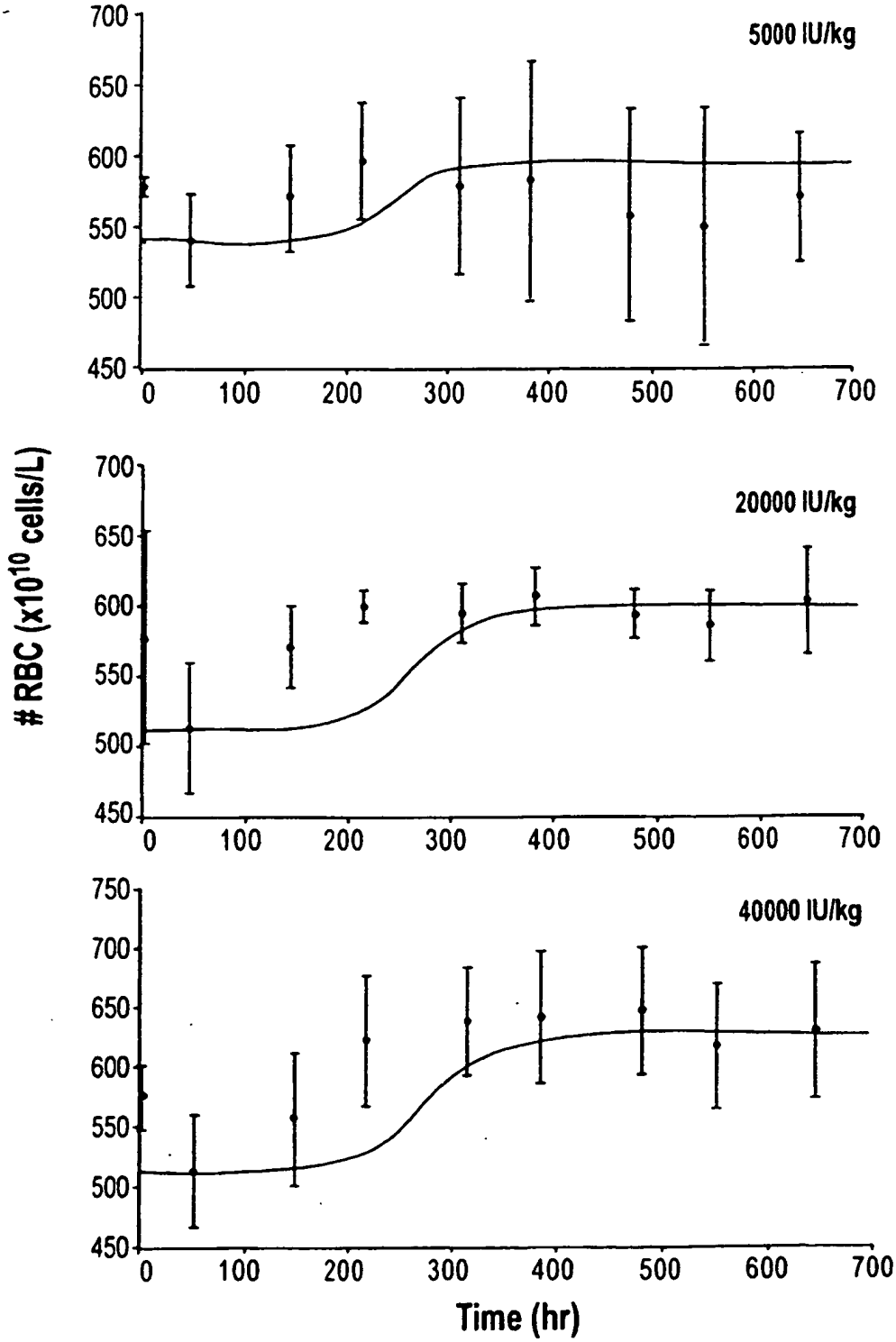

5000 IU/kg
20000 IU/kg
40000 IU/kg
RBC (x10^10 cells/L)
Time (hr)
700
650
600
550
500
450
750
0
100
200
300
400
500
600
700

FIG. 78B

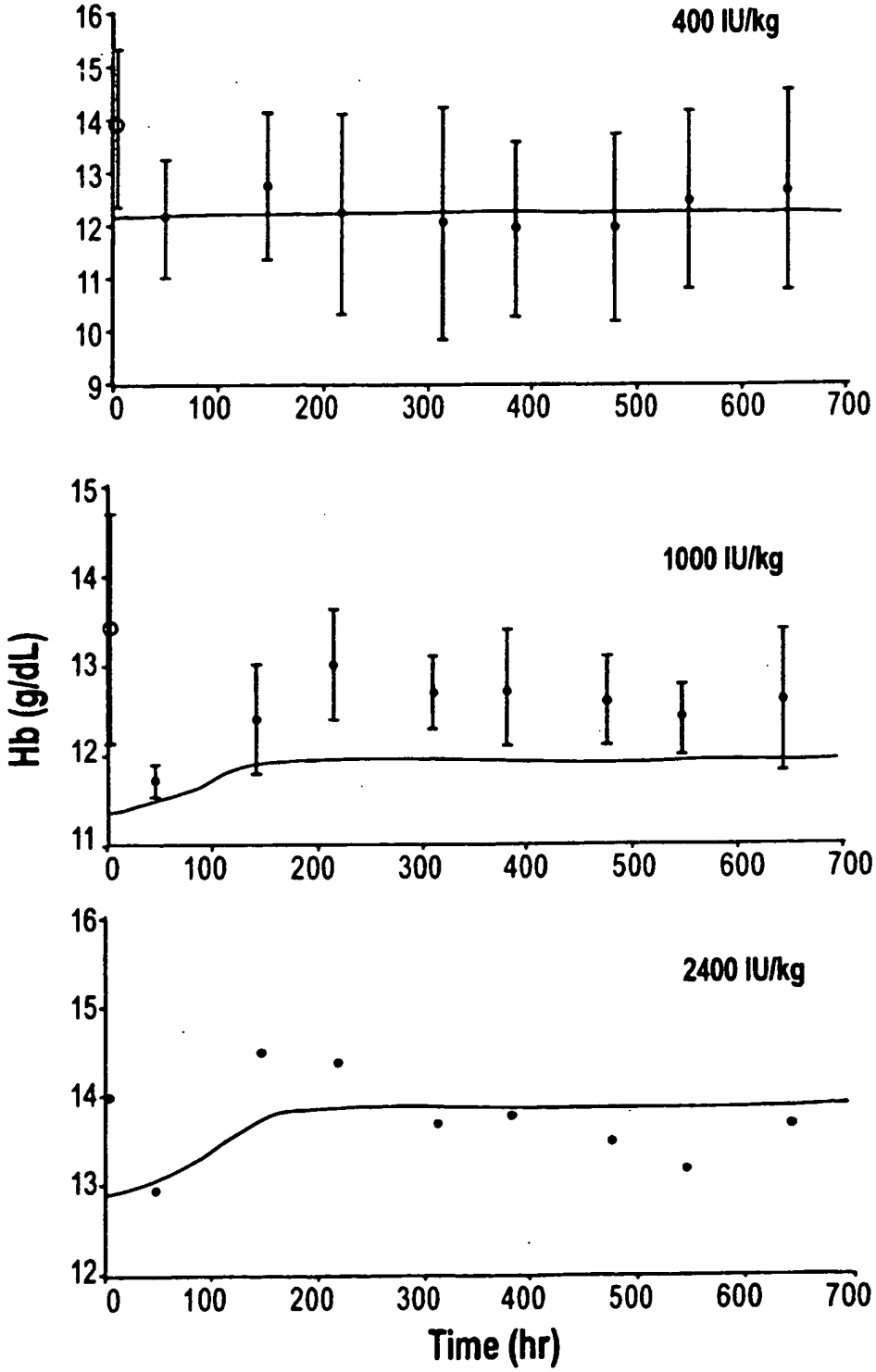

400 IU/kg
1000 IU/kg
2400 IU/kg
Hb (g/dL)
Time (hr)
16
15
14
13
12
11
10
9
0
100
200
300
400
500
600
700

FIG. 79A

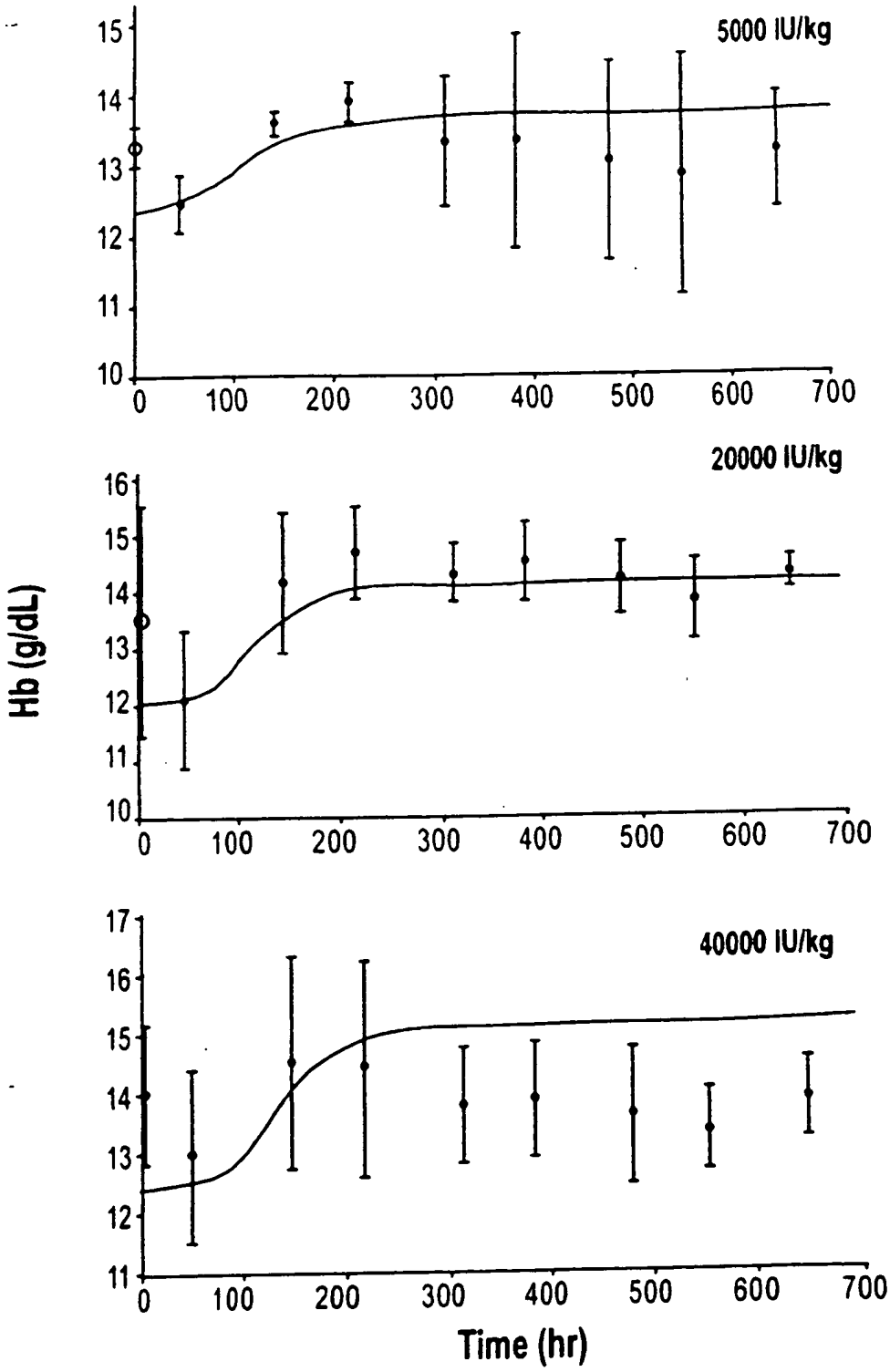

5000 IU/kg
20000 IU/kg
40000 IU/kg
Hb (g/dL)
Time (hr)
0
100
200
300
400
500
600
700

FIG. 79B

PHARMACODYNAMIC PARAMETERS IN HUMANS

	EPREX
TP1 (h)	88.17
TP2 (h)	10.76
RL (h)	116.6
Smax	4.251
SC50 (IU/L)	26.53
TP0 (h)	137.5
IC_{50} ($x10^{10}$ Reti/L)	38.71

FIG. 80

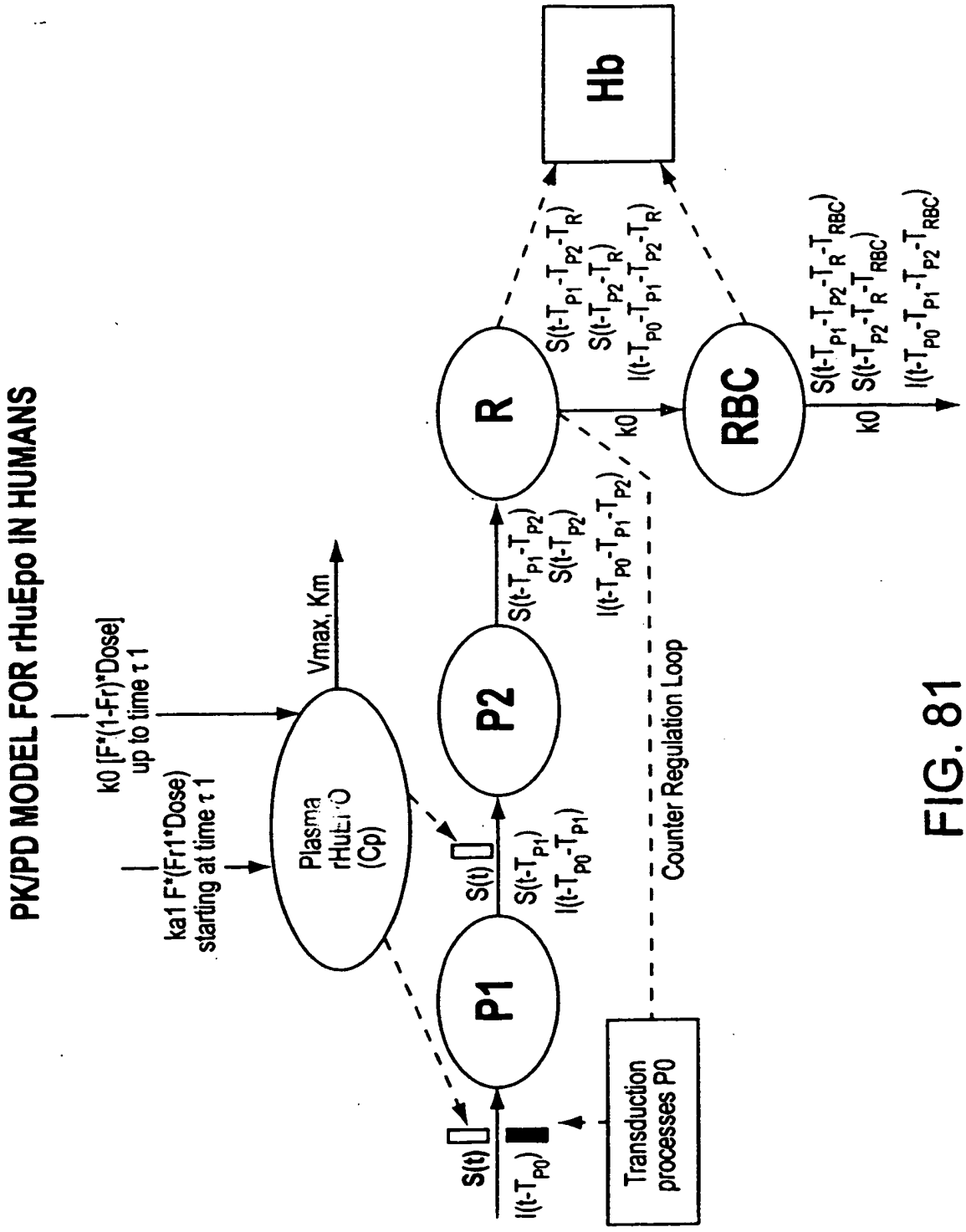

PK/PD MODEL FOR rHuEpo IN HUMANS
k0 [F*(1-Fr)*Dose]
up to time τ 1
ka1 F*(Fr1*Dose)
starting at time τ 1
Plasma
rHuEpO
(Cp)
Vmax, Km
P1
P2
R
RBC
Hb
S(t)
I(t-T_P0)
S(t-T_P1)
I(t-T_P0-T_P1)
S(t-T_P1-T_P2)
S(t-T_P2)
I(t-T_P0-T_P1-T_P2)
S(t-T_P1-T_P2-T_R)
S(t-T_P2-T_R)
I(t-T_P0-T_P1-T_P2-T_R)
S(t-T_P1-T_P2-T_R-T_RBC)
S(t-T_P2-T_R-T_RBC)
I(t-T_P0-T_P1-T_P2-T_RBC)
k0
Transduction
processes P0
Counter Regulation Loop

FIG. 81